UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	**Civil Action No. 3:16-md-2738-FLW-LHG** **MDL No. 2738**
THIS DOCUMENT RELATES TO ALL CASES	

THE PLAINTIFFS' STEERING COMMITTEE'S MEMORANDUM OF LAW IN RESPONSE AND OPPOSITION TO DEFENDANTS JOHNSON & JOHNSON AND JOHNSON & JOHNSON CONSUMER, INC.'S MOTION TO EXCLUDE PLAINTIFFS' EXPERTS' OPINIONS RELATED TO BIOLOGICAL PLAUSIBILITY

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The Plaintiff Steering Committee ("PSC") respectfully submits this memorandum in opposition to Defendants Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s (together, "J&J") motion to exclude the PSC's experts' opinions related to biological plausibility (Dkt. No. 9736-1) ("Motion" or "Def. Mot.").[1] For the foregoing reasons, this Court should deny J&J's Motion.

I. INTRODUCTION

J&J's Motion misconstrues the standards for biological plausibility and *Daubert*. Biological plausibility asks "whether the hypothesized causal link is credible in light of what is known from science and medicine about the human body and the potentially offending agent."[2] Proof of a mechanism, however, is not required under *Daubert* or to prove causation.[3] Rather, a biological plausibility opinion is admissible if, based on the scientific and medical literature, there is a

[1] This opposition specifically relates to the biological plausibility opinions of Drs. Shawn Levy, Judith Zelikoff, Arch Carson, Daniel Clarke-Pearson, Sarah Kane, Anne McTiernan, Patricia Moorman, Laura Plunkett, Jack Siemiatycki, Sonal Singh, Rebecca Smith-Bindman, Ellen Blair Smith, and Judith Wolf. Mot. at 1 n.1.

[2] *Milward v. Acuity Specialty Pods. Group*, 639 F.3d 11, 25 (1st Cir. 2011).

[3] Sir Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proc R Soc Med* 58(5): 295-300, at p. 298 (1965) (attached as **Exhibit 115**); *Ruiz-Troche v. Pepsi Cola of Puerto Rico Bottling Co.*, 161 F.3d 77, 86 (1st Cir. 1998) (courts should not impose "a standard of scientific certainty . . . beyond that which *Daubert* envisions").

plausible biological explanation for how the exposure of interest (here, perineal use of talcum powder) might result or contribute to the outcome (ovarian cancer).

The PSC's experts' opinions on biological plausibility are reliable. Based on their review of the peer-reviewed scientific and medical literature in its totality, the PSC experts opine that it is biologically plausible for J&J's talcum powder products[4] to increase the risk of epithelial ovarian cancer[5] because: (1) talcum powder is capable of getting to the fallopian tubes and ovaries either through migration from the perineum or through inhalation, and (2) once there, talcum powder causes

[4] *Johnson's Baby Powder* and *Shower-to-Shower*.

[5] It is customary to consider epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer as a single entity due to their common clinical behavior, risk factors, and pathogenesis. "The inclusion of FTC [fallopian tube cancer] within the ovarian epithelial cancer designation is generally accepted because of much evidence that points to a common Müllerian epithelium derivation and similar management of these three neoplasms." National Cancer Institute PDQ (attached as **Exhibit 113**); *see also* American College of Obstetricians and Gynecologists (ACOG): Ovarian Cancer FAQs (attached as **Exhibit 1**); ACOG/Society of Gynecologic Oncologists (SGO) Practice Bulletin Hereditary Breast and Ovarian Cancer Syndrome (2017) ("Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer.") (attached as **Exhibit 2**); Rule 26 Expert Report of Judith Wolf, M.D. ("Wolf Rep.") at 3 (attached as **Exhibit 3**); Rule 26 Expert Report of Ellen Blair Smith, M.D. ("Smith Rep.") at 2-3 (attached as **Exhibit 4**) ; Rule 26 Expert Report of Daniel L. Clarke-Pearson, M.D. ("Clarke-Pearson Rep.") at 3 (attached as **Exhibit 5**); Rule 26 Expert Report of Arch Carson, M.D., Ph.D. ("Carson Rep.") at 3 (attached as **Exhibit 6**); Rule 26 Expert Report of Rebecca Smith-Bindman, M.D. ("Smith-Bindman Rep.") at 11 (attached as **Exhibit 7**).

chronic inflammation and oxidative stress, which increases the risk of epithelial ovarian cancer.

These opinions are not based on "magic[]" or "fantasy."[6] These opinions are supported by the totality of long-standing peer-reviewed literature on migration of particulates within the female genital tract or through inhalation, the known carcinogenic constituents in talcum powder (including platy talc, asbestos, fibrous talc, heavy metals, fragrances, and other chemicals), and the known role inflammation and oxidative stress play in the pathogenesis of ovarian cancer. J&J's Motion to exclude these opinions fails for several reasons.

First, the PSC's experts fully appreciate the existence of different subtypes of epithelial ovarian cancer to the extent relevant. However, because of their similarities, particularly with respect to etiology, J&J's own experts and the scientific community often refer to epithelial ovarian cancer as one disease. Still, the PSC's experts acknowledge and discuss the subtypes and differences among them, and in reviewing the literature and giving their opinions also distinguish among the subtypes, where indicated.

Second, the PSC's experts' opinion that talcum powder can reach the fallopian tubes and ovaries when used on the perineum is based on the overwhelming body of peer-reviewed evidence that demonstrates that particulates readily migrate

[6] Def. Mot. at 1, 3.

from the vagina to the fallopian tubes, ovaries, and peritoneal surfaces,[7] and when inhaled, can enter the bloodstream and lymphatic system and then travel to the ovaries.

Confusing biological plausibility with some concept of "proof," J&J ignores the relevant evidence, arguing that migration is impossible because there is no migration study looking precisely at the perineal application of talcum powder. Biological plausibility and *Daubert* do not require such proof. Given the overwhelming body of relevant evidence, the PSC's experts reliably opine that migration can and does occur. Indeed, J&J's own experts concede that based on the evidence, migration is possible.[8] J&J's criticisms about individual migration studies go to the weight of the PSC's experts' opinions, not their admissibility.

Third, the PSC's experts' opinion that talcum powder can cause chronic inflammation and oxidative stress, which lead to an increased risk of ovarian cancer, also is based on reliable peer-reviewed scientific evidence. The connection between

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[7] The peritoneum is the serous membrane that lines the cavity of the abdomen and covers abdominal organs.

[8] March 27, 2019 Deposition of Kevin Holcomb M.D. ("Holcomb Dep.") at 421:23-422:12 ("[I]f you're saying is it possible, I'd have to say yes.") (attached as **Exhibit 8**); March 13, 2019 Deposition of Cheryl Saenz, M.D. ("Saenz Dep.") at 209:7-14 ("I do think that in terms of biologic plausibility, there is some data that there can be particulate matter that can make it to the ovaries, but I don't actually know one way or another if talc can do that.") (attached as **Exhibit 9**); March 19, 2019 Deposition of Benjamin G. Neel, M.D., Ph.D. ("Neel Dep.") at 270:2-8 (testifying that evidence on migration is "inconclusive") (attached as **Exhibit 10**).

inflammation and cancer has been known and widely accepted for decades. The scientific literature also is clear that inflammation plays an important role in the pathogenesis of epithelial ovarian cancer through a mechanism of cell proliferation, oxidative stress, DNA damage, and gene mutations. Given talcum powder's constituents and their documented ability to create an inflammatory response, the mechanism for increasing the risk of epithelial ovarian cancer is plausible.

At most, J&J and its experts simply offer different opinions based on the same evidence and quibble with the PSC's experts' reliance on and interpretation of specific studies. These challenges go to the weight of the evidence and are dealt with on cross-examination, not exclusion under *Daubert*.[9]

Finally, J&J seeks to exclude Dr. Zelikoff's opinions due to alleged plagiarism. J&J completely ignores the relevancy of explanations in Dr. Zelikoff's expert report and fails to otherwise explain why a lack of quotations citing background information make the opinions of a well-qualified toxicologist unreliable. Dr. Zelikoff's opinions on biological plausibility are well supported by reliable evidence and are her own. Her credibility should be determined by the jury.

J&J's Motion on biological plausibility should be denied in its entirety.

II. LEGAL STANDARDS ON BIOLOGICAL PLAUSIBILTY OPINIONS

[9] *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 596 (1993); *Karlo v. Pittsburgh Glass Works, LLC*, 849 F.3d 61, 81 (3d Cir. 2017); *In re TMI Litigation*, 193 F.3d 613, 664, 665 (3d Cir. 1999); *Milward*, 639 F.3d at 22.

The PSC incorporates the *Plaintiffs' Steering Committee's Omnibus Brief Regarding Daubert Legal Standard and Scientific Principles for Assessing General Causation*[10] and highlights the following important points of particular relevance to the outcome J&J's motion on biological plausibility.

Biological plausibility asks whether given what we know about the disease in question and possible pathogenic mechanisms, does the association make sense.[11] Biological plausibility is not the same as biological proof or certainty.[12] Here, the question is whether given what we know about epithelial ovarian cancer and talcum powder (which includes platy talc, asbestos, fibrous talc, heavy metals, and other chemicals),[13] does ovarian cancer from perineal use of talcum powder make sense.

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[10] Dkt. No. 9732 (hereinafter "*PSC's Omnibus Brief*").

[11] Hill (1965), at p. 298; Oleckno, "Epidemiology: Concepts and Methods," (1st ed. 2008) at p. 189 (attached as **Exhibit 117**); Rothman et al., "Modern Epidemiology," (3d Ed. 2008) at p. 28-29 (attached as **Exhibit 116**); *Milward*, 639 F.3d at 25.

[12] *In re Abilify (Aripiprazole) Prods. Liab. Litig.*, 299 F. Supp. 3d 1291, 1308 (N.D. Fla. 2018) ("[B]iological plausibility is not the same as biological certainty."); Michael D. Green, *et al.*, *Reference Manual on Scientific Evidence*, at 604-05 (3d Ed. 2011); April 9, 2019 Deposition of Gregory B. Diette, M.D. ("Diette Dep.") at 419:4-12 (attached as **Exhibit 11**) (J&J's expert testifying that biological plausibility "doesn't have to be proved").

[13] *See The Plaintiff Steering Committee's Opposition Defendants' Motion to Exclude Plaintiffs' Experts' Asbestos-Related Opinions*, *The Plaintiff Steering Committee's Opposition to Defendants' Motion to Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals and Fragrances in Johnson's Baby Powder and Shower to Shower*, and *The Plaintiff Steering Committee's Opposition to Defendants' Motion to Exclude Plaintiffs' Experts' General Causation Opinions*, all concurrently filed herewith.

The PSC's experts' opinions on whether this is biologically plausible are admissible so long as they are based on reliable scientific and medical knowledge and reasoning.[14] However, the PSC's experts "need not prove the biological means by which [talcum powder] acts in the body."[15] Instead, "where a hypothesis has been deemed plausible and credible in the relevant medical literature. . .it is reasonable to admit that hypothesis."[16] The PSC's experts are "not required to show that a mechanism has been definitely established. Instead [they] just need[] to show that the methodology [they] used to arrive at [their] opinion is sufficiently reliable."[17] Reliance on reliable scientific literature is a reliable method for determining

[14] *Allison*, 184 F.3d at 1319 n.23 ("While scientific testimony need not be known to a certainty, *Daubert* does require that assertions be derived from scientific knowledge."); *Milward*, 639 F.3d at 25.

[15] *In re Abilify*, 299 F. Supp. 3d at 1308; *In re Neurontin*, 612 F. Supp. 2d at 149 *In re PPA Prods. Liab. Litig.*, 289 F. Supp. 2d at 1247; *Fosamax*, 645 F. Supp. 2d at 183; *In re Fosamax Prods. Liab. Litig.*, No. 11-5304, 2013 WL 1558697, *3 (D.N.J. Apr. 10, 2013) (Pisano, J.) (fact that mechanism had not "been proven with human data" was not fatal to opinion).

[16] *Bartoli v. Novartis Pharm.*, 2014 WL 1515870, *7 (M.D. Pa. Apr. 17, 2014); *see also In re Zoloft Prods. Liab. Litig.*, 26 F. Supp. 3d 466, 469-70 (E.D. Pa. 2014) (finding a plausible mechanism of action where Zoloft "may" produce the adverse outcomes); *In re Fosamax*, 2013 WL 1558697 at *3 (defining biological plausibility as "coherence with existing knowledge").

[17] *In re Fosamax*, 2013 WL 1558697 at *6 (citing *Milward*, 639 F.3d at 15); *In re Roundup Prods. Liab. Litig.*, No. 16-MD-02741-VC, 2018 WL 3368534, at *17 (N.D. Cal. July 10, 2018).

biological plausibility.[18] Ultimately, it is the jury's role to determine whether the proposed mechanism is correct, not the court's.[19]

While biological plausibility is one of nine considerations in a Bradford Hill general causation analysis, it is not required. As Sir Bradford Hill explained: "It will be helpful if the causation we suspect is biologically plausible. But this is a feature I am convinced we cannot demand. What is biologically plausible depends upon the biological knowledge of the day…In short, the association we observe may be one new to science or medicine and we must not dismiss it too light-heartedly as just too odd."[20] Accordingly, "[w]hen mechanistic evidence is presented it can greatly strengthen a causal inference, but when it is absent it does not necessarily undermine

[18] *In re Fosamax*, 2013 WL 1558697 at *6; *In re Roundup*, 2018 WL 3368534 at *17; *Karlo*, 849 F.3d at 81; *In re Avandia Mktg. Sales Practices and Prods. Liab. Litig.*, No. 2007-MD-1871, 2011 WL 13576, at *9 (E.D. Pa. Jan. 4, 2011) (admitting expert testimony where "hypotheses about plausible mechanisms are based on scientific data about both the links between Avandia and lipid profiles and the connections between lipid profiles and outcomes").

[19] The standard for reliability "is 'lower than the merits standard for correctness.'" *Karlo*, 849 F.3d at 81 (quoting *In re TMI Litig.*, 193 F.3d at 665).

[20] Hill (1965), at p. 298; *see also Milward*, 639 F.3d at 25 (finding district court erred when "it conflated the scientific question of biological plausibility with the legal question of probability"); *In re Fosamax*, 2013 WL 1558697 at *6 (noting that "[o]ne or more of the factors may be absent even where a causal relationship exists and…no factor is a *sine qua non* of causation").

the inference."[21] However, "[t]he fact that the mechanism remains unclear does not call the reliability of the opinion into question."[22]

The PSC's experts' biological plausibility opinions readily meet these standards.

III. BIOLOGICAL PLAUSIBILITY OPINIONS AT ISSUE

The PSC's experts opine that there is a biologically plausible mechanism by which talcum powder causes ovarian cancer because (1) talcum powder can migrate or translocate to the fallopian tubes, ovaries and peritoneal surfaces from perineal use, and when inhaled, can enter the bloodstream and lymphatic system and then travel to the ovaries, and (2) once there, induce chronic inflammation and oxidative stress, which increases the risk of ovarian cancer. The PSC's experts' opinions are reliable and well-supported by the following medical and scientific literature. Each of the PSC's experts' opinions on biological plausibility is based on and consistent with the following evidence.

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[21] *In re Denture Cream Prods. Liab. Litig.*, 795 F. Supp. 2d 1345, 1356 (S.D. Fla. 2011).

[22] *In re PPA Prods. Liab. Ligi.*, 289 F. Supp. 2d 1230, 1247 (W.D. Wash. 2003); *see also In re Fosamax Prods. Liab. Litig.*, 645 F. Supp. 2d 164, 183 (S.D.N.Y. 2009) ("That the mechanism remains unknown does not mean that the one proposed by the [plaintiffs' expert] is not widely acceptable as plausible."); *In re Neurontin Mktf. Sales Practices and Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 149 (D. Mass. 2009) (biological plausibility supported causation opinion despite "robust debate in the scientific community" on the proposed mechanism).

A. THE MEDICAL AND SCIENTIFIC LITERATURE SUPPORT THE OPINION THAT TALCUM POWDER CAN MIGRATE TO THE OVARIES, FALLOPIAN TUBES, AND PERITONEAL SURFACES

There are two biological mechanisms by which talcum powder reaches the ovaries, fallopian tubes, and peritoneum to cause ovarian cancer. The first is through migration from perineal application.

It is generally accepted in the medical and scientific literature that substances can migrate upward from the vagina to the fallopian tubes, ovaries, and peritoneum. J&J's own experts concede that once in the vagina, particulate matter can make it to the ovaries.[23]

One known biological mechanism for transporting particles upward from the vagina to the fallopian tubes and ovaries is uterine peristalsis – rhythmic contractions in the female genital tract that occur regularly through a woman's menstrual cycle.[24]

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[23] Saenz Dep. at 209:7-14; *id.* at 217:4-5 ("There is a way that you can pass up through the cervix once something is in the vagina."); Holcomb Dep. at 421:23-422:12; Neel Dep. at 270:2-8.

[24] Jones, Richard E. and Kristen H. Lopez, "Human Reproductive Biology," at 162 (4th Ed. 2006) ("[D]ead sperm reach the oviduct at about the same time as do live sperm. Thus, sperm tail beating probably is not important during sperm transport through the uterus, so it must be the muscle contraction and movement of cilia in the female reproductive tract that facilitate sperm transport.") (attached as **Exhibit 114**); Kissler et al., "Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement," *Acta Obstet Gynecol Scand* 83: 369-374, 369-70 (2004) (recognizing that contractions occur through a woman's cycle) (attached hereto as **Exhibit 12**); Kunz et al., "The Uterine Peristaltic Pump Normal and Impeded Sperm Transport within the Female Genital Tract," *The Fate of the Male Germ Cell* 49: 267-277, at p. 269

"During menstruation, contraction waves with the lowest frequency are directed towards the cervix, while during other phases of the cycle, with the highest frequency and intensity during the periovulatory phase, cervico-fundal peristalsis [upward contraction] prevails."[25] Peristalsis has been observed to occur at a rate of 1.2-2.8 contractions per minute, depending on the phase of a woman's cycle.[26] Additionally, retrograde menstruation – the upward movement of menstrual blood through the fallopian tubes – is well-documented and occurs in up to 90% of women.[27]

(1997) ("Since the velocity of sperm movement does not itself account for covering such a long distance through the female genital tract within a few minutes, rapid sperm transport is considered a passive phenomenon and has been ascribed to uterine contractions.") (attached hereto as **Exhibit 13**); Zervomanolakis et al., "Physiology of Upward Transport in the Human Female Genital Tract," *Ann. N.Y. Acad. Sci.* 1101: 1-20, at p. 1 (2007) (discussing uterus and fallopian tubes as "functionally united peristaltic pump") (attached hereto as **Exhibit 14**).

J&J's gynecologic oncologist expert Dr. Holcomb concedes genital peristalsis exists. Holcomb Dep. at 437:23-438:11; *see also* Wolf Rep. at 10; Clarke-Pearson Rep. at 7; Rule 26 Report of Laura M. Plunkett, Ph.D., DABT ("Plunkett Rep.") at 28, 35-36 (attached as **Exhibit 15**); January 9, 2019 Deposition of Ellen Blair Smith, M.D. ("Smith Dep.") at 262:21-263:7 (attached as **Exhibit 16**); Carson Rep. at 7; Smith-Bindman Rep. at 35.

[25] Kissler et al. (2004) at pp. 369-370.

[26] Kunz et al. (1997) at p. 269; Henderson et al., "The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat," *Env. Res.* 40: 247-250, at p. 247 (1986) ("The rhythmic muscular contractions of the uterus that occur spontaneously and the illicit currents established by the epithelial cells of the genital tract may contribute to the translocation process.") (attached as **Exhibit 17**).

[27] Halme et al., "Retrograde Menstruation in Healthy Women and in Patients with Endometriosis," *Obst. & Gyn.* 64: 151-154, at p. 153 (1984) (observing retrograde menstruation in 90% of study patients and concluding that "the fallopian tubes play

It is not surprising then, that upward migration of particulates through the female genital tract occurs. For example, cornstarch from surgical gloves used during gynecological examinations was found in the cervical canal, uterine cavity and fallopian tubes within 24 hours and up to 4 days after the exam.[28] The study authors concluded that "[t]his study has pointed out a retrograde migration of starch also in humans after a gynecological examination with powdered gloves[;] [c]onsequently, powder or any other potentially harmful substances that can migrate from the vagina should be avoided."[29]

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an important role as conduits for menstrual blood") (attached hereto as **Exhibit 18**); Blumenkrantz et al., "Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis," *Obstetrics & Gynecology* 57(5): 667-670, at p. 669 (1981) ("[R]etrograde bleeding regularly occurs with menstruation in most if not all women on peritoneal dialysis and quite possibly in most menstruating women in the general population.") (attached hereto as **Exhibit 19**); *see also* Wolf Rep. at 10; Plunkett Rep. at 28; Smith Dep. at 318:13-319:6 ("a majority of women experience retrograde menstruation").

[28] Sjosten et al., "Retrograde migration of glove powder in the human female genital tract," *Human Reprod.* 19: 991-995, at p. 995 (2004) (attached hereto as **Exhibit 20**).

[29] *Id.* at pp. 991; *id.* at 994 (concluding that the study in humans confirmed what had been previously observed in animals); *see also*, *e.g.*, Rule 26 Expert Report of Patricia G. Moorman, MSPH, Ph.D. ("Moorman Rep.") at 33 (attached as **Exhibit 21**); Clarke-Pearson Rep. at 8; Smith Rep. at 16; Wolf Rep. at 11; Carson Rep. at 7; Smith-Bindman Rep. at 35; Plunkett Rep. at 28; Rule 26 Expert Report of Anne McTiernan, M.D., Ph.D. ("McTiernan Rep.") at 59 (attached hereto as **Exhibit 22**); Rule 26 Expert Report of Sonal Singh ("Singh Rep.") at 57 (attached as **Exhibit 23**); Rule 26 Expert Report of Judith Zelikoff ("Zelikoff Rep.") at 12 (attached as **Exhibit 24**).

Similarly, particulate radioactive material was observed in the ovaries and fallopian tubes of 14 of 21 study patients within 24 hours after being placed in the vagina.[30] The study authors noted that "[i]f transit can take place so easily, it is probably the same for many chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties."[31]

Carbon particles also were observed in the fallopian tubes of two of three patients within 28 and 34 minutes, respectively, after being placed in the posterior fornix.[32] The study authors concluded that the data confirm that "[c]ontractions of

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[30] Venter and Iturralde, "Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries," *S. Afr. Medi. J.* 55: 917-919, at pp. 918, 919 (1979) (attached hereto as **Exhibit 25**). The radioactive material was placed in the vagina with the patient laying on her back with her buttocks slightly elevated and her legs closed; the patient remained in this position for two hours; images were obtained 4-24 hours later. *Id.* at pp. 917-918; *see also*, *e.g.*, Rule 26 Expert Report of Jack Siemiatycki MSc, Ph.D. ("Siemiatycki Rep.") at 30 (attached as **Exhibit 26**).

[31] *Id.* at p. 919; *see also* Iturralde and Venter, "Hysterosalpingo-Radionuclide Scintigraphy (HERS)," *Sem. in Nuc. Med.* 11(4): 301-314, at pg. 301 (1981) (**Exhibit 27**) ("Access of talc to the peritoneal cavity is most likely through the vagina."); Zervomanolakis et al. (2007) at pp.6-7 (labeled particles were detected in the uterine cavity within two minutes of placement in vagina and "[u]ptake into the uterus" of all patients, and in one or both fallopian tubes of 79% of patients).

[32] Egli and Newton, "The Transport of Carbon Particles in the Human Female Reproductive Tract," *Fert. & Ster.* 12: 151-155, at p. 153 (1961) (attached hereto as **Exhibit 28**). The carbon particles were suspended in dextran and placed at the posterior fornix as the women laid downward at a 15° angle and were given oxytocin to aid in contractions. *Id.* at p. 152. Upward migration resulted. *Id.* at 153.

the muscle of the uterus or other reproductive organs" encourage upward migration of sperm and other particulates.[33]

Although these studies did not specifically look at whether particulates applied to the perineum (as opposed to the vagina) can migrate to the ovaries or fallopian tubes, they are highly relevant and instructive because it is universally accepted in the medical and scientific literature that "[t]alc placed on the perineum may enter the vagina and ascend to the upper genital tract."[34] That is because normal

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[33] *Id.* at 154.

[34] Folkins, A., Elke A Jarboe, Jonathan L. Hecht, Michael G. Muto, and Christopher P. Crum, "Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy," *Diagnostic Gynecologic and Obstetric Pathology*, at p. 846 (3d Ed. 2017) (attached as **Exhibit 29**); *see also* Health Canada, Draft Screening Assessment, Talc, Environment and Climate Change Canada (Dec. 2018) at p. 21 ("This evidence of retrograde transport supports the biological plausibility of the association between perineal talc application and ovarian exposure. . . .") (attached as **Exhibit 30**); Schildkraut et al., "Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)," *Cancer Epidemiol. Biomarkers Prev.* 25: 1411-1417, at p. 1415 (2016) ("As most high-grade serous EOC, but not nonserous subtypes, arise in the fallopian tube, it is possible that direct exposure through the genital tract specifically effects this disease subtype.") (attached as **Exhibit 31**); Houghton et al., "Perineal Powder Use and Risk of Ovarian Cancer," *JNCI* 106: 1-6, at p. 1 (2014) ("Talc particulates from perineal application have been shown to migrate to the ovaries.") (attached as **Exhibit 32**); Langseth et al., "Perineal use of talc and risk of ovarian cancer," *J. Epidemiol. Comm. Health* 62: 358-360, at p. 358 (2008) ("A majority of women experience retrograde menstruation; this suggests a mechanism by which talc can travel through the female production tract to the ovaries.") (attached as **Exhibit 33**); Henderson et al., at p. 247 (1986) ("Direct communication between the external environment and the peritoneal cavity exists in the female via her genital tract."); Merritt et al., "Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer," *Int. J. Cancer*, 122: 170-176, at p. 174 (2008) ("[I]t has been demonstrated experimentally that talc particles can reach the ovaries in humans

activities such as walking, vaginal intercourse, use of tampons, going to the bathroom, and exercise, can easily move particulates from the perineum to the vagina.[35] In addition, the particles studied in the migration literature are similar in size and other chemical and morphologic features to those found in talcum powder products.[36]

As a result, the FDA states that the "potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable."[37] Similarly, the International Agency for Research on Cancer ("IARC") states: "Consumer products (e.g. cosmetics, pharmaceuticals) are the primary sources of exposure to talc for the

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and rodents as the result of talc use in the pelvic region….") (attached as **Exhibit 34**); *See also* Clarke-Pearson Rep. at 7; Wolf Rep. at 10.

[35] January 7, 2019 Deposition of Dr. Judith Wolf ("Wolf Dep."), at 194:7-195:20 (attached as **Exhibit 35**); Huncharek et al., "Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies," *Euro. J. of Cancer Prev.* 16(5): 422-429, at p. 423 (2007) (recognizing that "in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position") (attached as **Exhibit 36**); Heller et al., "Asbestos Exposure and Ovarian Fiber Burden," *Am. J. of Indust. Med.* 29: 435-439, at p. 438 (1996) (proposing sexual intercourse as a "transporting vector for asbestos fibers" to the ovaries) (attached as **Exhibit 37**).

[36] Health Canada Assessment at p. 9 (recognizing that the particles studied in Egli et al. (1961), DeBoer, "Transport of Particulate Matter Through the Human Female Genital Tract", *J. Reprod. Fert.* 28, 295-297 (1972) (attached as **Exhibit 38**), and Venter and Iturralde (1979) are "the same size as talc.").

[37] April 1, 2014 FDA Response to Citizen's Petition (attached as **Exhibit 39**).

general population. Inhalation and dermal contact (i.e. through perineal application of talcum powder) are the primary routes of exposure."[38]

J&J's biological plausibility expert Dr. Michael Birrer also agrees that "[t]he vagina serves as a portal to the internal reproductive tract," the vagina "is a reproductive conduit in all respects, connecting the external environment to the internal genitalia," and the reproductive tract is "in most women, an open conduit."[39] Dr. Birrer also testified in previous litigation consistent with the PSC's experts here:

> Any material – whether it be talc, heavy metals, asbestos, whatever – can migrate from the perineum to the ovaries through the reproductive tract. There's an anatomical conduit. So it's not like it's blocked. Theoretically, it could happen.[40]

Pathological studies also confirm the presence of talc and asbestos (constituents of talcum powder) in human ovarian cells and lymph nodes, further supporting the opinion that particulates such as talcum powder can and do migrate

[38] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, "Arsenic, Metals, Fibres, and Dusts Volume 100 C A Review of Human Carcinogens," (2012) at 232 (hereinafter, "IARC 2012") (relevant portions attached as **Exhibit 40**).

[39] Ex. 9 to Birrer Dep. (attached hereto as **Exhibit 41**); March 29, 2019 Deposition of Michael Birrer, M.D., Ph.D. ("Birrer Dep.") at 124:24-125:23, 129:21-130:3 (attached as **Exhibit 42**); *see also* Clarke-Pearson Rep. at 7; Wolf Rep. at 10; Smith Rep. at 17.

[40] September 25, 2018 Deposition of Michael Birrer, M.D., *Brower, et al. v. Johnson & Johnson, Inc. et al.*, at 96:22-97:8 (attached as **Exhibit 43**).

within the human body.[41] In Henderson et al. 1971, talc particles were found "deep within" or "embedded" in the human tissue samples from 10 out of 13 ovarian tumors, 12 out of 21 cervical tumors, and 5 out of 21 normal ovaries.[42]

In two separate studies by Heller et al. in 1996, talc was identified in human ovarian tissue samples of women who reported perineal talcum powder use[43] and asbestos was identified in 9 of 13 women that were exposed to asbestos.[44] The

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[41] Gertig et al., "Prospective Study of Talc Use and Ovarian Cancer," *J. of the Nat'l Cancer Inst.* 92(3): 249-252, at p. 252 (2000) ("Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue, although no relation between reported levels of talc exposure and ovarian talc counts has been observed.") (attached as **Exhibit 44**); Cramer et al., "Genital Talc Exposure and Risk of Ovarian Cancer," *Int. J. Cancer* 81: 351-356, at p. 356 (1999) ("It has been demonstrated that inert particles contaminating the vagina can reach the ovaries [and] [t]alc has been found in both normal and malignant ovarian tissue.") (attached as **Exhibit 45**); Langseth et al. (2008) at p. 358 ("From pathological studies it is known that particles and fibres that enter the body can migrate to distant organs."); Siemiatycki Rep. at 65; Moorman Rep. at 33; Smith-Bindman Rep. at 35; Plunkett Rep. at 28; Wolf Rep. at 11; Clarke-Pearson Rep. at 8; Singh Rep. at 57.

[42] Henderson et al., "Talc and Carcinoma of the Ovary and Cervix," *The Journal of Obstetrics and Gynaecology* 78: 266-272, at pp. 266-268 (1971) (attached as **Exhibit 46**).

[43] Heller et al., "The relationship between perineal cosmetic talc usage and ovarian talc particle burden," *Am. J. Obstet. Gynecol.* 174: 1507-1510, at p. 1509 (1996) (attached as **Exhibit 47**); Zelikoff Rep. at 13-14; Wolf Rep. at 10; Clarke-Pearson Rep. at 8; McTiernan Rep. at 58-59; Moorman Rep. at 33; Siemiatycki Rep. at 65; Plunkett Rep. at 29; Singh Rep. at 57; Rule 26 Expert Report of Sarah Kane, M.D. ("Kane Rep.") at 14 (attached as **Exhibit 48**).

[44] Heller et al. "Asbestos Exposure and Ovarian Fiber Burden" *American Journal of Industrial Medicine* 29:435-439 (1996), at p. 437 (attached as **Exhibit 49**); *see also* Mostafa et al., "Foreign Body Granulomas in Normal Ovaries," *Obstetrics and Gynecology* 66: 701-702, at p. (1985) (of all women operated on at Johns Hopkins

authors concluded that "[t]he detection of talc in all the ovaries demonstrates that talc can reach the upper genital tract"[45] from perineal use and that "women with a positive exposure history had asbestos detected in their ovaries more frequently."[46]

Talc particles also have been found in human pelvic lymph nodes of women that used talcum powder on their genitals. Cramer et al. 2007 identified talc in three of four lymph nodes of a women who reported using talcum powder in her genital area daily for 30 years.[47] Very recently, McDonald et al. 2019 examined pelvic lymph nodes of users and non-users of genital talcum powder and found "the level of talc in nodal tissue at least five times higher in those who used talc genitally compared to those who had not," confirming "earlier observations that talc particles, from perineal exposure, can and do migrate to pelvic lymph nodes."[48] The migration

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Hospital for pelvic disease, 9% had magnesium silicate (commonly found in talc and asbestos) granulomas in their ovaries and another 9% had "histologic entities that were very similar") (attached as **Exhibit 50**).

[45] Heller et al. (1996-talc) at pp. 1509-1510.

[46] Heller et al. (1996-asbestos) at p. 439.

[47] Cramer et al., "Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc," *Obstetrics & Gynecology* 110(2): 498-501, at p. 499 (2007) (attached as **Exhibit 51**); *see also* Kane Rep. at 14; McTiernan Rep. at 59; Moorman Rep. at 33.

[48] McDonald et al., "Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes," *Ultrastructural Pathology* 43: 13-27, at pp. 21, 24 (2019) (attached as **Exhibit 52**).

literature together with the presence of talc and asbestos in ovarian tissue and lymph nodes sufficiently supports the migration of talcum powder within the genital tract.[49]

Finally, the scientific literature supports inhalation as another route of exposure to talcum powder.[50] Talcum powder's size and consistency puts women who use it at risk for inhalation exposure.[51] Health Canada measured talcum powder particles to determine whether they are within the respirable range and concluded that "all of the particles were within the inhalable range" and "the median particle size was within the respirable range. . . ."[52]

In its 2012 Monograph on asbestos, IARC concluded that all forms of asbestos, including asbestiform talc or fibrous talc, are Group 1 carcinogens and

[49] Animal studies provide further support for the migration of talcum powder through the genital tract. *See* Keskin, et al., "Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study," *Arch Gynecol Obstet* 280: 925-931, at p. 926 (2009) (attached as **Exhibit 53**); Henderson et al. (1986) at p. 247.

[50] *See* Wolf Rep. at 11; Clarke-Pearson Rep. at 8; Zelikoff Rep. at 14-17; Singh Rep. at 57-58; Plunkett Rep. at 27-28; Moorman Rep. at 33; Siemiatycki Rep. at 65; Kane Rep. at 14.

[51] Steiling et al., "Principles for the safety evaluation of cosmetic powders," *Tox. Letters* 297: 8-18, at p. 12 (2018) (recognizing that loose powders, including baby powder, "could generate such a dust cloud or atmosphere during product handling or application, and therefore there is the potential for inhalation exposure") (attached as **Exhibit 54**); Zelikoff Rep. at 15 (discussing particle size).

[52] Health Canada Draft Assessment at p. 23.

cause ovarian cancer through inhalation.[53] IARC stated "that a causal association between exposure to asbestos and cancer of the ovary was clearly established" based on occupational exposure studies and further supported by environmental exposure studies.[54] In so concluding, IARC recognized that inhalation through use of talcum powder on the perineum is a primary route of exposure.[55]

Additionally, IARC acknowledged that inhaled asbestos travels to other parts of the body through the lymphatic system.[56] Asbestos and fibrous talc fibers can migrate across the diaphragm through the peritoneal cavity and penetrate the ovaries, and once fibers have entered the interstitium, they also have access to the vascular and lymphatic systems.[57] Accordingly, the evidence shows that inhaled asbestos and

[53] IARC 2012 at 219, 232, 256, 280; Diette Dep. at 391:16-392:4 (IARC concluded asbestos causes ovarian cancer).

[54] *Id.* at 256. Importantly, IARC "considered the possibility that cases of peritoneal mesothelioma may have been misdiagnosed as ovarian cancer" but found insufficient evidence of misclassification. *Id.*

[55] *Id.* at 232.

[56] IARC 2012 at 280 ("The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals."); *see also* Cramer et al. (2007) (talc found in lymph nodes).

[57] Kane et al., "Mechanisms of Fibre Carcinogenesis," IARC Scientific Publications No. 140, at pp. 12, 25 (1996) (attached as **Exhibit 55**).

fibrous talc (which are contained in talcum powder) can reach the peritoneal cavity and ovaries and contribute to the development of ovarian cancer.[58]

B. THE MEDICAL AND SCIENTIFIC LITERATURE SUPPORT THE OPINION THAT TALCUM POWDER CAUSES CHRONIC INFLAMMATION AND OXIDATIVE STRESS THAT LEADS TO AN INCREASED RISK OF OVARIAN CANCER

Once talcum powder gets to the ovaries, fallopian tubes, or peritoneum the scientific evidence reveals that it elicits an inflammatory response and induces oxidative stress, which increases the risk of ovarian cancer through a well described process that ultimately results in DNA damage and genetic mutations.

Numerous peer-reviewed studies have concluded that talcum powder causes an inflammatory response that increases the risk of ovarian cancer.[59] As Gates et al.

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[58] Health Canada Draft Assessment at p. 22 ("There is a potential for inhalation exposure to talc powder during the use of certain self-care products (e.g., cosmetics, natural health products, non-prescription drugs formulated as loose powders)."); Cramer et al. (2007) (finding talc in lymph nodes suggests migration through inhalation); IARC 2012 at 280; Wolf Rep. at 11 (concluding that "inhalation of these particles is another recognized route of exposure" and citing IARC 2012, Longo et al. 2017, Steiling (2018), and Cramer (2007)); Clarke-Pearson Rep. at 8 (concluding that "inhalation is another possible mechanism" and citing IARC 2012 and Steiling (2018)); Zelikoff Rep. at 14-17; Singh Rep. at 57-58; Plunkett Rep. at 27-28; Siemiatycki Rep. at 65; Kane Rep. at 14.

[59] *See, e.g.*, Penninkilampi, et al., *Perineal Talc Use and Ovarian Cancer*, Epidemiology 29: 41–49, 45 (2018) ("If chronic inflammation due to ascending foreign bodies is indeed the mechanism by which talc is associated with increased ovarian cancer, then these results fit the picture.") (attached as **Exhibit 56**); Mills et al., "Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California," *Int'l J. Cancer* 112(3): 458-464, at p. 458 (2004) ("Collectively, these studies point to a possible etiologic role of talc in ovarian cancer via an inflammatory

(2008) explained: "Normal ovarian cells treated with talc are more likely to undergo cell proliferation and neoplastic transformation, and cellular generation of reactive oxygen species increases with increasing exposure to talc."[60] Similarly, Health Canada concluded, "[t]here is support for an association of inflammation and increased risk of ovarian cancer."[61]

Balkwill, a world-renowned cancer researcher identified talcum powder use as an inflammatory stimulus related to ovarian cancer in 2001.[62] Although J&J

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process at the site of the ovarian epithelium.") (attached as **Exhibit 57**); Wu et al., "Markers of inflammation and risk of ovarian cancer in Los Angeles County," *Int. J. Cancer* 124: 1409-1415, at p. 1414 (2009) ("Our findings on talc and endometriosis are consistent with previous findings and are compatible with the hypothesis that these factors increase the risk of ovarian and that inflammation may be a common pathway.") (attached as **Exhibit 58**) ; Merritt et al. (2008), at p. 170 ("Indeed the most consistent evidence linking inflammation with ovarian cancer comes from the many reports that use of talc in the perineal region increases ovarian cancer risk."); Taher et al., "Systematic Review and Meta-Analysis of the Association between Perineal Use of Talc and Risk of Ovarian Cancer," *unpublished* at p. 26 (2018) ("Chronic inflammatory response and alteration in local immunogenicity are possible mechanisms" for talcum powder causing ovarian cancer") (attached as **Exhibit 59**).

[60] Gates et al., "Talc use, variants of the GSTM1, GSTT1, and NAT2 genes and risk of epithelial ovarian cancer," *Cancer Epidemiol Biomarkers Prev.* 17(9): 2436-2444, at p. 2443 (2008) (attached as **Exhibit 60**).

[61] Health Canada Draft Assessment at p. 18 ("With respect to talc specifically, local irritation leading to an inflammatory response is one of the possible mechanisms of tumour progression that is frequently hypothesized…There is support for an association of inflammation and increased risk of ovarian cancer.").

[62] Balkwill and Mantovi (2001), "Inflammation and cancer: back to Virchow?" *The Lancet* 357: 539-545 at p. 539, Table 1 (identifying "[p]elvic inflammatory

claims this study is "outdated,"[63] a citation search on Google Scholar reveals that the article has been cited over 2300 times since 2015, providing solid evidence that it is certainly not considered outdated by the scientific community. Moreover, numerous researchers subsequently have opined that talcum powder is an inflammatory mediator that contributes to ovarian cancer.[64]

The science supports these conclusions. *First*, the link between chronic inflammation and ovarian cancer is well-supported.[65] "[D]espite being a designed

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disease/***talc***/tissue remodeling" as "[i]nflammatory stimulus" that are associated with ovarian cancer) (emphasis added) (attached as **Exhibit 61**).

[63] Def. Mot. at 62, n.152.

[64] *See supra* n.59.

[65] *See, e.g.*, Balkwill, F. and A. Mantovani, , at p. 539 (2001) (recognizing that as far back as 1863, inflammatory cells (leukocytes) were identified in tumor tissue); *id.* ("increased risk of malignancy is associated with the chronic inflammation caused by chemical and physical agents") Coussens, L. and Zena Werb, "Inflammation and Cancer," *Nature* 420: 860-867, at Table 1 (2002) (listing "[p]elvic inflammatory disease, chronic cervicitis" as pathological conditions associated with "[o]varian carcinoma, cervical/anal carcinoma") (attached as **Exhibit 62**); Okada, F., "Beyond foreign-body induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progressions," *Int. J. Cancer* 121: 2364-2372, at p. 2364 (2007) ("[T]umor development and progression are accelerated inevitably by inflammation caused from foreign bodies, and that reactive oxygen species derived from inflammatory cells are one of the most important genotoxic mediators to accelerate the process.") (attached as **Exhibit 63**); Liou and Storz, "Reactive oxygen species in cancer," *Free Radical Research* 44:479-496, at p. 479 (2010) ("Elevated rates of reactive oxygen species (ROS) have been detected in almost all cancers, where they promote many aspects of tumour developments and progression.") (attached as **Exhibit 64**); Grivennikov et al., "Immunity, Inflammation, and Cancer," *Cell.* 140(6): 883-988, at p. 883 (2010) ("A role for inflammation in tumorigenesis is now generally accepted, and it has become evidence that an inflammatory microenvironment is an essential component of all

response to eliminate pathogens and other agents harmful to the host, the inflammation when deregulated or inappropriately maintained has the potential to cause injury, necrosis, and malignant transformation."[66] "Chronic inflammation is induced by biological, chemical, and physical factors and is in turn associated with an increased risk of several human cancers."[67]

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tumors, including some which a direct causal relationship with inflammation is not yet proven.") (attached as **Exhibit 65**); Crusz and Balkwill, "Inflammation and cancer: advances and new agents," *Nature* 12: 584-596, at p. 584 (2015) ("Chronic, dysregulated, persistent, and unresolved inflammation is associated with an increased risk of malignant disease.") (attached as **Exhibit 66**); Reuter et al., "Oxidative stress, inflammation, and cancer: How are they linked?" *Free Radic Biol Med.* 49(11): 1603-1616 (2010) (recognizing that oxidative stress and chronic inflammation increase the risk of cancer) (attached as **Exhibit 67**); Kiraly et al., "Inflammation, DNA Damage and Mutations *In Vivo*," *PLO Genetics* 11: 1-24 at p. 2 (2015) (attached as **Exhibit 68**); Trabert et al., "Pre-diagnostic levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial," *Gynecol Oncol.* 135(2): 297-304, at pp. 298, 309 (2014) ("Epidemiological evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer….Our study provides additional evidence that inflammation plays an important roles in ovarian carcinogenesis.") (attached as **Exhibit 69**); National Academic of Sciences, Engineering, and Medicine (2016), *Ovarian cancers: Evolving paradigms in research and care*, Washington DC: The National Academic Press. (attached as **Exhibit 70**).

[66] Fernandes et al., "The Role of the Mediators of Inflammation in Cancer Development," *Pathol. Oncol. Res.* 21: 527-534, at p. 527 (2015) (attached as **Exhibit 71**).

[67] Reuter et al. (2010) at p. 2; Crusz and Balkwill (2015) at p. 584 ("Almost 20% of human cancers are related to chronic inflammation caused by infections, exposure to irritants or autoimmune disease."); Coussens and Werb (2002) at p. 4.

Chronic inflammation is associated with various stages of cancer development, including initiation, growth, and metastasis.[68] All cancers are caused by genetic mutations, including epithelial ovarian cancer.[69] Chronic inflammation leads to genetic mutations through cell proliferation, oxidative stress, and DNA damage.[70] Inflammatory environments contain cytokines and chemokines that contribute to cancer growth.[71] Inflammatory environments also generate reactive oxygen species ("ROS") and reactive nitrogen species ("RNS") that are actively mutagenic and cause DNA damage.[72]

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[68] Balkwill and Mantovi (2001), at p. 539; Reuter et al. (2010) at p. 5.

[69] Clarke-Pearson Dep. at 92:16-21 (attached as **Exhibit 72**); Rule 26 Expert Report of Shawn Levy, Ph.D. ("Levy Rep.") at 3 ("[C]ancer is caused by changes (mutations) to the DNA within cells.") (attached as **Exhibit 73**).

[70] *See* Coussens and Werb (2002), at p. 4 ("Functionally, many promoters, whether directly or indirectly, induce cell proliferation, recruit inflammatory cells, increase production of reactive oxygen species leading to oxidative DNA damage, and reduce DNA repair."); Okada (2007) at p. 2369 ("Inflammatory environments due to the existence of foreign body cause a variety of biological responses as they contain increased growth/survival factors, chemotactic cytokines (chemokines), matrix metalloproteases, adhesion molecules, extracellular matrix, inflammatory mediators (i.e., histamine, eicosanoids, inflammatory cytokines and proteases, DNA-damage-promoting agents (i.e., ROS and RNS) and augmented angiogenesis."); Fernandes et al. (2015), at p. 528 ("[I]t is well established that chronic inflammation is strongly associated with several human cancers, since it leads to the release of pro-inflammatory cytokines, and other immunomodulatory, creating a favorable microenvironment for tumor progression and metastasis.").

[71] Coussens and Werb (2002), at p. 4; Okada (2007) at p. 2369.

[72] Yan et al., "Molecular analysis of genetic instability," *Cancer* 512: 15-28, at p. 16 (2009) (inflammation induces ROS which causes "genetic aberrations and leads to transformation") (attached as **Exhibit 74**); Hanahan, D. and Robert A. Weinberg,

This inflammation cascade is shown to occur in the pathogenesis of epithelial ovarian cancer.[73] The tumor environment in which epithelial ovarian cancer develops has a broad spectrum of pro-inflammatory cytokines and chemokines.[74] "At sites of inflammation, epithelial cells are exposed to increased levels of

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"Hallmarks of Cancer: The Next Generation," *Cell* 144: 646-674, at p. 659 (2011) ("[I]nflammatory cells can release chemicals, notable reactive oxygen species, that are actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy.") (attached as **Exhibit 75**); Okada (2007) at p. 2369; Clarke-Pearson Rep. at 4; Wolf Rep. at 12; Smith Rep. at 17; Levy Rep. at 11; Singh Rep. at 58; Zelikoff Rep. at 22-24; Siemiatycki Rep. at 65.

[73] Savant et al., "The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer," *Cancers* 10, 251: 1-30., at Figure 1 (2018) ("Unresolved, chronic inflammation is a critical risk factor in [ovarian] tumor initiation.") (attached as **Exhibit 76**); Ness, Roberta B. and Carrie Cottreau, "Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer," *J. of the Nat'l Cancer Inst.* 91: 1459-1467, at p. 1463 (1999) (attached as **Exhibit 77**); JNJ 00000704 (Sept. 30, 2004 Fax from Luzenac Director of Product Safety to Bill Ashton from JNJ discussing Ness as offering "some compelling evidence in support of the 'migration' hypothesis") (attached as **Exhibit 78**); Saed et al., "Updates on the role of oxidative stress in the pathogenesis of ovarian cancer," *Gynecologic Oncology* 145: 595-602, at p. 596-97 (2017) (attached as **Exhibit 79**); Shan, W. and Jinsong Liu, "Inflammation: A hidden path to breaking the spell on ovarian cancer," *Cell Cycle* 8(19): 3107-3111, at p. 3110 (2009) ("Increasing evidence suggests that inflammation contributes significantly to the etiology of EOC.") (attached as **Exhibit 80**); Saed, Morris and Fletcher (2018), "New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress," *Ovarian Cancer – From Pathogenesis to Treatment* Chapter 4 (attached as **Exhibit 81**).

[74] Freedman et al., "Peritoneal inflammation – A microenvironment for Epithelial Ovarian Cancer (EOC)," *J. of Translational Med.* 2: 1-10, at p. 4 (2004) (attached as **Exhibit 82**); Shan and Liu (2009), at p. 3110 ("The tumor milieu in which EOC develops has been described as one enriched with a broad spectrum of pro-inflammatory cytokines and chemokines.")

inflammatory mediators such as reactive oxygen species [ROS], cytokines, prostaglandins, and growth factors that contribute to increased cell division, and genetic and epigenetic changes."[75]

The following from Savant et al. 2018 depicts the inflammatory environment whereby chronic inflammation from talcum powder exposure and other possible factors expose the ovary to ROS production, oxidative stress, cytokines and growth factors, generating an inflammatory response that results in additional and repeated ROS and cytokines:

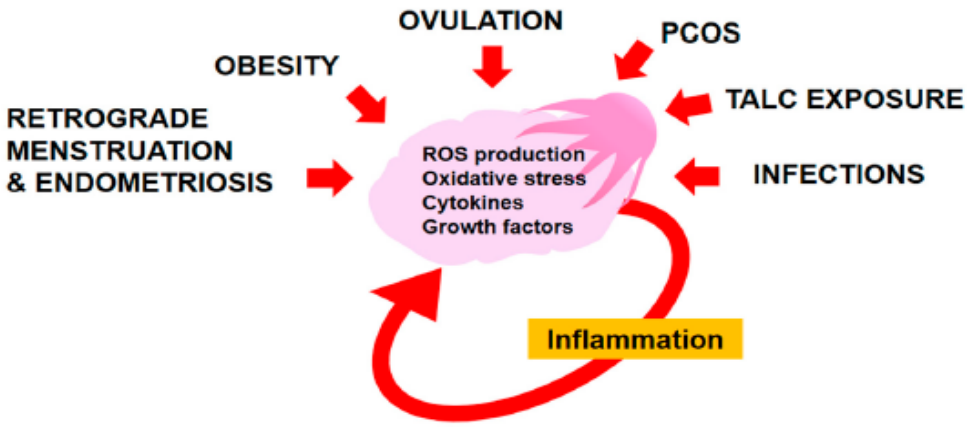

Figure 1. Sources of inflammation in the ovary and fimbriae. Ovulation, retrograde menstruation, endometriosis, infections, exposure to talc, Polycystic Ovarian Syndrome (PCOS), and obesity result in exposure of the ovary and fimbriae to reactive oxygen species (ROS), oxidative stress, cytokines, and growth factors, generating an inflammatory response that leads to additional production of ROS and cytokines in the ovary. Unresolved, chronic inflammation is a critical risk factor for tumor initiation.

[75] Savant et al. (2018), at p.1.

Furthermore, studies in which generation of ROS was inhibited showed cell death to proceed normally,[76] further supporting the role of ROS (and thus, inflammation) in increased cell growth and cancer progression. Myeloperoxidase also is released by epithelial ovarian cancer cells in response to inflammation and is indicated to play a role in the progression of carcinogenesis by promoting cell death.[77] Inhibiting myeloperoxidase likewise leads to normal cell death.[78]

[76] Jiang, Z., Nicole M. Fletcher, Rhouba Ali-Fehmi, Michael P. Diamond, Husam M. Abu-Soud, Adnan R. Munkarah, and Ghassan M. Saed, "Modulation of redox signaling promotes apoptosis in epithelial ovarian cancer cells," *Gynecol Oncol.* 122(2): 1-17, at p. 8 (2011) (attached as **Exhibit 83**); *see also* Belotte et al. 2014, "The Role of Oxidative Stress in the Development of Cisplatin Resistance in Epithelial Ovarian Cancer," *Reproductive Sciences* 21(4): 503-508, at p. 505-506 (2014) (attached as **Exhibit 84**).

[77] Fletcher, N., Zhonglian Jiang, Rhouba Ali-Fehmi, Nancy K. Levin, Jimmy Belotte, Michael A. Tainsky, Michael P. Diamond, Hasam M. Abu-Soud, and Ghassan M. Saed, "Myeloperoxidase and free iron levels: Potential biomarkers for early detection and prognosis of ovarian cancer," *Cancer Biomarkers* 10:267-275, at p. 268 (2011) (attached as **Exhibit 85**); Saed et al., "Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer," *Gynecol Onco.* 116(2): 1-14, at p. 6 (2010) (attached as **Exhibit 86**).

[78] Fletcher, Saed et al. (2011), at p. 268.

Second, asbestos and fibrous talc are known carcinogens that cause ovarian cancer.[79,] J&J's own experts agree that talc and asbestos cause chronic inflammation and that asbestos is carcinogenic.[80]

Additionally, *in vitro* and *in vivo* studies have shown that talc and asbestos cause inflammation and oxidative stress in human and animal cells.[81] *In vitro* studies

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[79] IARC 2012 at pp. 219, 232, 256, 280; *see also* Reid et al., "Gynecologic and Breast Cancers in Women After Exposure to Blue Asbestos in Wittenoom," *Cancer Epidemiology, Biomarkers & Prevention* 18: 140-147 (2009) (attached as **Exhibit 87**). For a more detailed description, see the *Plaintiffs' Steering Committee's Memorandum In Response And Opposition To Johnson & Johnson And Johnson & Johnson Consumer Inc.'s Motion To Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals And Fragrances In Johnson's Baby Powder And Shower-To-Shower* and *The Plaintiff Steering Committee's Memorandum of Law in Response and Opposition to Defendant's Johnson & Johnson and Johnson & Johnson Consumer Inc.'s Motion to Exclude the Plaintiffs' Experts' Asbestos-Related Opinions,* both of which are being filed simultaneously and are incorporated herein.

[80] Holcomb Dep. at 174:11-18 (concedes that talc causes chronic inflammation); *see also* Huncharek et al., (2007) at p. 427 ("If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogenic effect as it contains a known carcinogen.").

[81] Radic et al., "Immunosuppression induced by talc granulomatosis in the rat," *Clin. Exp. Immunol.* 73: 316-321 (1988) (talc granulomas initiated whole-animal immune suppression in rats) (attached as **Exhibit 88**); National Toxicology Program, "Toxicology and Carcinogenesis Studies of Talc," U.S. Dept. of Health and Human Servs., No. 421 at pp. 11, 56 (1993) (in inhalation study of talc "[t]here was clear evidence of carcinogenic activity of talc in female" rats and finding "principal toxic lesions associated with inhalation exposure to the same concentrations of talc in rats included chronic granulomatous inflammation") (attached as **Exhibit 89**); Keskin et al. (2009) at p. 926 (foreign body reaction, infection and increased inflammatory cells were found in all rats exposed to talc); Kahn et al., "Nano-talc Stabilized TNF-m-RNA I Human Macrophages," *J of Biomedical Nanotechnology* 7: 112-113, at p.113 (2011) ("Observations clearly demonstrated the inflammatory potential of

also document inflammatory and pro-carcinogenic biologic effects in cell cultures exposure to talcum powder. These studies include Shukla[82] (demonstrating genotoxicity in both asbestos and nonfibrous talc), Buz'Zard[83] (demonstrating aberrant ROS [reactive oxygen species] and neoplastic transformation), Akhtar[84]

[nano talc] particles which might be at least partial and potential mechanism in talc mediated pathogenicity in the exposed population.") (attached as **Exhibit 90**); Ghio et al., "Disruption of Iron Homeostasis in Mesothelial Cells after Talc Pleurodesis," *Am J Respi Cell Mol Biol* 46: 80-86, at p. 80 (2012) ("[E]xposure to talc was associated with a time-dependent and concentration-dependent generation of oxidants in both cells types. The expression of proinflammatory mediators was also increased after *in vitro* exposures of mesothelial and airway epithelial cells to talc.") (attached as **Exhibit 91**); Akhtar et al., "Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells," *Environmental Tox* 394-406, at p. 404 (2012) (talc particles "significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells") (attached as **Exhibit 92**); Levy Rep. at 14; Smith Rep. at 17; Clarke-Pearson Rep. at 4; Wolf Rep. at 12; Zelikoff Rep. 24-25; Plunkett Rep. at 42-43; Moorman Rep. at 34; Singh Rep. at 59; Siemiatycki Rep. at 65; McTiernan Rep. at 60-61; Carson Rep. at 5.

[82] Shukla, Arti, Maximilian B. MacPherson, Jedd Hillegass, Maria E. Ramos-Nino, Vlada Alexeeva, Pamela M. Vacek, Jeffrey P. Bond, Harvey I. Pass, Chad Steele, and Brooke T. Mossman, "Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity," *American Journal of Respiratory Cell and Molecular Biology* 41:114-123 (2009) (attached hereto as **Exhibit 93**).

[83] Buz'Zard and Lau, "Pycnogenol reduces Talc-induced Neoplastic Transformation in Human Ovarian Cell Cultures," *Phytother. Res.* 21: 579-586, at p. 585 (2007) (attached hereto as **Exhibit 94**) ("The data show that talc is capable of increasing cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells.").

[84] Akhtar et al. (2012) at p. 404 (talc particles "significantly induced cytotoxicity, oxidative stress, and apoptosis in human lung epithelial cells").

(demonstrating induced cytotoxicity, oxidative stress, and apoptosis), and Akhtar[85] (demonstrating toxicity mediated through oxidative stress). Saed and his colleagues expand this body of literature by exposing 5-6 cell lines including normal fallopian tube and ovarian cells, as well as ovarian cancer cells, to *Johnson's Baby Powder*, finding alteration in the redox state indicating oxidative stress, elevation in CA-125 levels, enhanced cell proliferation, inhibited apoptosis, changes in gene expression, and inducement of SNPs (single nucleotide polymorphisms) in a dose-responsive fashion.[86] These studies provide important evidence of the effects of talcum powder at the molecular level.

IV. THE PSC'S EXPERTS' BIOLOGICAL PLAUSIBILITY OPINIONS ARE RELIABLE AND ADMISSIBLE

As discussed above, the PSC's experts' biological plausibility opinions are based on robust data demonstrating that: (a) particulates similar to talcum powder readily migrate upwards in the genital tract from the vagina to the ovaries, fallopian tubes, and peritoneal cavity; (b) inhaled particulates (including asbestos and fibrous

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[85] Akhtar, et al. "The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid." *Toxicology in Vitro: An International Journal Published in Association with BIBRA* 24, no. 4 (June 2010): 1139–47 (attached hereto as **Exhibit 95**).

[86] Fletcher, NM, Amy K. Harper, MD, Ira Memaj, BS, Rong Fan, MS, Robert T. Morris, MD, and Ghassan M. Saed, PhD. "Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer." Reproductive Sciences 1-10. (2019) (attached hereto as **Exhibit 96**).

talc) can reach the ovaries through the blood stream and lymphatic system; (c) once at the ovaries and fallopian tubes, talcum powder causes chronic inflammation and oxidative stress, which leads to DNA damage and increases the risk of ovarian cancer. Rather than address the evidence in its totality, J&J focuses on a handful of studies, arguing that these studies do not support biological plausibility. J&J's arguments are without merit and do not justify exclusion under *Daubert*.

A. THE PSC'S EXPERTS APPROPRIATELY CONSIDER EPITHELIAL OVARIAN CANCER SUBTYPES

J&J first accuses the PSC's experts of failing to consider the different subtypes of ovarian cancer in their biological plausibility opinions. This is untrue and a red-herring. While there are different epithelial ovarian cancer subtypes, there are many commonalities including the etiology among them.[87] This is why much of the scientific evidence discusses epithelial ovarian cancer as a single disease, particularly with regard to causal factors such as inflammation.[88]

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[87] *See* Wolf Rep. at 3 ("Epithelial carcinoma of the ovary, fallopian tube, and peritoneum are usually considered as a single entity due to their common clinical behavior, risk factors, and pathogenesis."); Smith Rep. at 2-3; Clarke-Pearson Rep. at 3; National Cancer Institute PDQ; American College of Obstetricians and Gynecologists (ACOG): Ovarian Cancer FAQs; ACOG/Society of Gynecologic Oncologists (SGO) Practice Bulletin Hereditary Breast and Ovarian Cancer Syndrome (2017) ("Based on the contemporary understanding of the origins and management of ovarian cancer and for simplicity in this document, ovarian cancer also refers to fallopian tube cancer and primary peritoneal cancer.").

[88] *See*, *e.g.*, Savant et al. (2018) at p. 2 (discussing inflammation as a risk factor for all epithelial ovarian cancer subtypes); Balkwill and Mantovani at p. 539 (identifying

Nonetheless, to the extent relevant, the PSC's experts considered the different subtypes of epithelial ovarian cancer and formed their opinions accordingly.[89] The PSC's expert Dr. Levy explained:

> Q: Is your opinion related to all the different histologic types of epithelial ovarian cancer?
>
> A: My -- my opinion is not exclusive to any -- any one type. Certainly, the epithelial serous being the more common and most virulent type of cancers I think represents the most common. From a mechanistic perspective, I mentioned some of the other subtypes and the common gene mutations that go along with them and as, again, supportive of the same mechanism. And I think, if anything, the -- the current data would suggest a -- a higher prevalence of a particular subtype of cancer but certainly not the -- the mechanism doesn't -- is not exclusive to any one type.[90]

J&J also criticizes Dr. Saed's choice of macrophage cells and immortalized fallopian tube and ovarian epithelial cells for use in his research, claiming they are

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talcum powder as an "[i]nflammatory stimulus" for "ovarian" cancer); Shan and Liu (2009) at p. 3108 (discussing epithelial ovarian cancer as single entity for purposes of inflammation).

[89] Clarke-Pearson Rep. at 3, 4; Zelikoff Rep. at 19; McTiernan Rep. at 17; Moorman Rep. at 29; Smith Rep. at 2-3; Siemiatycki Rep. at 45-47; Wolf Rep. at 3; Smith-Bindman Rep. at 9-10; Clarke-Pearson Dep. at 132:12-133:17 (recognizing that different mechanisms can cause each subtype but that the evidence demonstrates talcum powder causes all subtypes except clear cell is uncertain because it is "a very rare cancer"); Smith Dep. at 242:5-19 (testifying that the subtypes are "poorly differentiated" and "overlapping").

[90] January 11, 2019 Deposition of Shawn Levy, Ph.D. ("Levy Dep.") at 259:4-260:8; *see also id.* at 260:9-18 (attached as **Exhibit 97**).

irrelevant. As is discussed in great detail in the *Plaintiff Steering Committee's Memorandum in Opposition to Johnson & Johnson and Johnson & Johnson Consumer, Inc.'s Motion to Exclude Expert Opinions of Ghassan Saed*, Dr. Saed's choice of cell lines is well supported in the literature. The medical literature supports the clinical relevance of molecules related to the cancer microenvironment in ovarian cancer stromal cells.[91] Normal immortalized ovarian epithelial cells are also relevant and frequently used for in vitro ovarian cancer studies.[92] The fact that these studies of human tissues showed inflammation and genetic transformation in human epithelial and fallopian tissues is relevant.

B. THE PSC'S EXPERTS' OPINIONS ON MIGRATION ARE SUPPORTED BY RELIABLE SCIENTIFIC AND MEDICAL LITERATURE

In an effort to distract from the overwhelming evidence on migration as a whole, J&J parses out individual studies and critiques them as being unsupportive of migration, despite the authors' contradictory conclusions.[93] J&J's effort to

[91] Davidson et al., "The Role of the Tumor Stroma in Ovarian Cancer," *Front Oncol.* 4: 104 (2014) (attached hereto as **Exhibit 98**).

[92] Shin et al., "Establishment of five immortalized human ovarian surface epithelial cell lines via SV40 T antigen or HPV E6/E7 expression," *PLOS One* 13(10): 1-16, at p. 1 (2018) (immortalized "human ovarian surface epithelial (HOSE) cells are a critical cell source for ovarian cancer research.") (attached as **Exhibit 99**).

[93] *Ref. Man.* at 600 (recognizing review of the "relevant available scientific evidence, taken as a whole" is proper, rather than "review [of] each scientific study individually"); *see also In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787, 796–797 (3d Cir. 2017) (citing *Milward*, 639 F.3d at 17 ("[t]he court

discredit some studies simply reveals that this is an issue of weight for the jury, not a basis for exclusion under *Daubert*.

1. The Presence of Talc and Asbestos in Reproductive Tissue Supports Migration

J&J first focuses on three studies showing the presence of talc in reproductive tissue – Henderson (1971), Cramer (2007), and Heller (1996-talc). J&J argues that these studies only show that talc "from some source can be found in human ovaries or lymph nodes" but do not prove migration.[94] This argument goes to the weight of the studies, not their ability to support the PSC's experts' opinion as part of the totality of the evidence.

While J&J may be correct that in isolation, these studies only prove that talc got to the ovaries and lymph nodes from somewhere, that is not how scientific evidence is reviewed or considered. Rather, when viewed through the lens of the totality of the evidence on the ability of particles to migrate upward from the vagina

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treated the separate evidentiary components of [the expert's] analysis atomistically, as though his ultimate opinion was independently supported by each."); *Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607 (D.N.J. 2002); *In re Tylenol (Acetaminophen) Mktg., Sales Practices, & Prod. Liab. Litig.*, 198 F. Supp. 3d 446, 458 (E.D. Pa. 2016); *In re Phenylpropanolamine (PPA) Prod. Liab. Litig.*, 289 F. Supp. 2d 1230, 1242 (W.D. Wash. 2003) (rejecting defense *Daubert* challenges which "isolate these sources [of evidence] rather than considering the whole").

[94] Def. Mot. at 22.

to the ovaries and fallopian tubes and through inhalation,[95] the presence of talc in the ovaries and lymph nodes has clinical and scientific significance.

J&J's only critique of these studies appears to be that the talc came from contamination. But J&J has no basis in fact for attributing the presence of talc solely to contamination. The study authors expressly controlled for contamination and noted that the talc was deeply embedded in the tissue, indicating it was not from contamination.[96] "Talc particles found, for example, *on* ovarian tissue might be contaminants deposited during sample collection and processing. For talc particles *in* the ovarian tissue, contamination during sample collection and processing can be ruled out."[97]

Additionally, as J&J recognizes, recent research, expressly designed to account for contamination, found talc in ovarian tissue and confirmed the "earlier

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[95] *See supra* §III.A. Notably, J&J ignores Heller et al. (1996–asbestos), which demonstrated the presence of asbestos in ovarian tissue and concluded that "women with a positive exposure history had asbestos detected in their ovaries more frequently." *Id.* at p. 439; Clark-Pearson Rep. at 8; Wolf Rep. at 10 of reliance list; Smith Rep. at 10 of reliance list.

[96] Heller et al. (1996-talc) at p. 1508 ("Routinely, all solutions are checked for detectable limits of contaminating particles; all places where particles could have contaminated the specimen, such as paraffin, are also controlled for."); Cramer (2007) at p. 500 ("talc was shown to be present in macrophages within the actual tissue, ruling out contamination during processing"); Henderson et al. (1971) at p. 268.

[97] Wehner et al., "Biological effects of cosmetic talc," *Fd Chem. Toxic* 32(12): 1173-1184, at p. 1175 (1994) (attached as **Exhibit 100**).

observations that talc particles, from perineal exposure, can and do migrate to pelvic lymph nodes."[98] These studies are reliable and support the PSC's experts' opinions.

2. The PSC's Experts' Migration Opinions Are Supported by Studies Showing Migration of Particles in the Female Genital Tract

J&J does not contend that the migration studies upon which the PSC's expert rely are unreliable. Instead, J&J argues that migration is not supported by the numerous human migration studies. According to J&J, those studies all "involved insertion of particles into the genital tract" (rather than perineal application), manipulation of the environment to encourage migration (rather than normal human behavior and even though the conditions represent normal and common occurrences in women e.g. lying down, increased oxytocin levels with orgasm, or insertion of particles as occurs with sexual intercourse or other daily activities). J&J also claims that particles other than talc are not relevant (even similar in size and other morphologic features).[99]

Again, these criticisms go to the weight of the evidence and opinion, not admissibility. The PSC's experts are not required to point to a study specifically showing the migration of talcum powder from the perineum to the fallopian tubes

[98] McDonald et. al (2019) at p.12; *see also* Mot. at 21 n.44 (citing McDonald).

[99] Def. Mot. at 24.

and ovaries to conclude that migration is plausible.[100] Nonetheless, J&J's critiques of the evidence are misplaced.

First, J&J completely ignores real life and female anatomy. Access to the vagina from the perineum does not require the moving of mountains that J&J suggests.[101] Among other things, women exercise, use the restroom, use tampons, lay down, and engage in sexual intercourse – all activities that can result in talcum powder that was applied to their perineum migrating or translocating into their vaginas.[102] For this reason, J&J's experts, the PSC's experts, regulatory authorities, and the medical and scientific community all agree that the outside world has access to the peritoneal cavity through the vagina, uterus and fallopian tubes.[103] Therefore,

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[100] *Milward*, 639 F.3d at 23; *In re Testosterone Replacement Therapy*, 2017 U.S. Dist. LEXIS 69399, *1005 (admitting expert testimony where there was no "single piece of evidence the experts rely upon [that] is sufficient to support their causation opinions. But the experts have adequately explained why they have reached their conclusions on the basis of the evidence as a whole.").

[101] *See* January 19, 2019 Deposition of Arch Carson ("Carson Dep.") at 301:16-302:2 (testifying that application to the perineum is equivalent to materials instilled into the vagina")(attached as **Exhibit 101**).

[102] Wolf Dep. at 194:7-195:20; Huncharek et al. (2009) at p. 423 (recognizing that "in the experimental setting translocation of talc particles to the human ovary can occur with deliberate or inadvertent manipulations of patients in the supine position"); Heller et al. (1996-asbestos) at p. 438 (proposing sexual intercourse as a "transporting vector for asbestos fibers" to the ovaries).

[103] Ex. 9 to Birrer Dep.; *see also* Clarke-Pearson Rep. at 7; Wolf Rep. at 10; Smith Rep. at 17; April 2014 FDA Letter; IARC 2012 at 232; Health Canada, Draft Screening Assessment, at p. 21 ("This evidence of retrograde transport supports the biological plausibility of the association between perineal talc application and ovarian exposure. . . ."); Folkins et al. at p. 846 ("Talc placed on the perineum may

studies that show migration from the vagina upward are relevant to whether powder placed on the perineum could similarly migrate once it gets in the vagina.

Second, the evidence is overwhelming that once in the vagina, particles rapidly migrate upward to the ovaries and fallopian tubes.[104] As the literature explains, uterine peristalsis (the regular and natural contractions that occur in the genital tract) creates contractions that result in upward migration of particles from the vagina to the ovaries and fallopian tubes.[105]

Sjosten et al. (2004), is particularly instructive on this point. In Sjosten, the study subjects received a "routine gynecological examination" by a doctor using cornstarch powdered gloves.[106] "Any medication that might have influenced the tubal patency [opening the fallopian tubes]" was not administered.[107] No other steps

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enter the vagina and ascend to the upper genital tract."); Houghton et al. (2014), at p. 1 ("Talc particulates from perineal applicable have been shown to migrate to the ovaries."); Langseth et al. (2008) at p. 358 ("A majority of women experience retrograde menstruation; this suggests a mechanism by which talc can travel through the female production tract to the ovaries."); Henderson et al. (1986), at p. 247 ("Direct communication between the external environment and the peritoneal cavity exists in the female via her genital tract.").

[104] *See supra* §III.A. (discussing evidence).

[105] Jones and Lopez at p. 162; Kissler et al. (2004) at p. 369-70; Kunz et al. (1997) at p. 269; Egli and Newton (1961) at p. 154.

[106] Sjosten et al. (2004), at p. 992.

[107] *Id.*

were taken to influence migration.[108] Yet, within 24 hours and for up to 4 days following examination, cornstarch was found in the cervical canal, uterine cavity, and fallopian tubes.[109] The study authors concluded that "[s]ince evidence suggests that a retrograde migration could be a general mechanism…we should be critical of harmful substances, e.g. glove powder, that could migrate from the vagina to abdominal cavity."[110] This study, in connection with the numerous other studies demonstrating migration and the tissue studies showing the presence of talc and asbestos, certainly support a biologically plausible mechanism through migration.

Finally, while the PSC's experts readily acknowledge the differences among the types of particulates used in the studies,[111] the type of particle does not appear to matter as all different types of particles (including cornstarch) behave the same by migrating upward. Additionally, it has been recognized that the particulates studied, are similar in size to talc.[112]

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[108] That the women in this study were laying down is not atypical of what women do in their daily lives. *See* Def. Mot. at 29 n. 57.

[109] *Id.* at p. 992-93, 995.

[110] *Id.* at 995.

[111] Wolf Rep. at 10-11; Smith-Bindman Rep. at 35; Smith Rep. at 16; Clarke-Pearson Rep. at 7-8; McTiernan Rep. at 58; Zelikoff Dep. at 427:21-429:3 (attached as **Exhibit 102**)(talcum powder particles are within the range of the particles used in the animal studies).

[112] Health Canada Assessment at p. 9 (recognizing that the particles studied in Egli et al. (1961), DeBoer (1972), and Iturralde and Venter (1979) are "the same size as talc.").

J&J also critiques the PSC's experts' reliance on animal studies.[113] Animal studies may be relied upon for purposes of biological plausibility.[114] Indeed, the cases cited by J&J recognize the important role animal data may play in determining human causation,[115] but involve situations where the experts relied solely on animal studies and were unable to explain how the results from those studies were appropriately extrapolated to humans.[116]

However, here, the PSC's experts rely on the extensive *human data* on migration discussed above, not on the handful of animal studies.[117] While Dr.

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[113] Def. Mot. at 32-40.

[114] *In re Testosterone Replacement Therapy*, 2017 U.S. Dist. LEXIS 69399, at *1015; *In re Actos (Pioglitazone Prods. Liab. Litig.*, No. 12-CV-00064, 2013 U.S. Dist. LEXIS 179235, at *12 (W.D. La. Dec. 19, 2013) (approving reliance on animal studies to show biological plausibility); *Smith*, 2011 U.S. Dist. LEXIS 47197, at *2 (admitting expert opinion that relied in part on in vitro and animal studies).

[115] *See In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 407 (S.D.N.Y. 2005) ("In addition to research on humans, scientists often perform experiments on living animals, such as rats, mice, and monkey. The advantages of such studies include the fact that they can be conducted as true experiments, with exposure controlled and measure and ethical limitations diminished.").

[116] *See* Def. Mot. at 35 (citing *GE v. Joiner*, 522 U.S. 136, 144-145 (1997) (plaintiff failed to explain "how and why the exerts could have extrapolated their opinions from these seemingly far-removed animal studies"); *Wade-Geaux v. Whitehall Labs., Inc.*, 874 F. Supp. 1441, 1482 (D.V.I. 1994) (experts failed to provide "any reasoned basis" for relying on animal studies)).

[117] *See* Clarke-Pearson Rep. at 7-8; Wolf Rep. at 10-11; Smith Rep. at 16-17; McTiernan Rep. at 58-59; Moorman Rep. at 33; Plunkett Rep. at 28; Zelikoff Rep. at 13-14; Carson Rep. at 6; Siemiatycki Rep. at 65; Singh Rep. at 18-19, 57; Smith-Bindman Rep. at 35; Levy Rep. at 14.

Zelikoff discusses the animal studies, she appropriately acknowledges their limitations when it comes to studying migration and simply notes that the animal data further supports her biological plausibility opinions.[118]

Oddly, while J&J critiques the use of animal data for purposes of opining on migration in humans, it also accuses the PSC's experts of "cherry-picking" for failing to consider a *single* animal study that J&J likes – Wehner et al. (1986).[119]

First, the PSC's experts did consider Wehner (1986) with the totality of the evidence.[120]

Second, Wehner (1986) does not disprove migration. The authors there simply concluded that based upon the limited study, "[i]t is less clear whether or not inanimate particles such as carbon black or talc can translocate of their own accord from the vagina to the oviducts and beyond."[121] Importantly, Wehner predated the majority of studies relied on by the PSC's experts, including Sjosten et al. (2004),

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[118] *See, e.g.*, Zelikoff Rep. at 13 ("Though animal studies have limitations due to the differences in anatomy, they provide evidence that talc can migrate through the reproductive system."); *id.* at 13-14 (discussing human data).

[119] Def. Mot. at 36-38 (discussing Wehner et al., "On Talc Translocation From the Vagina to the Oviducts and Beyond," *Food Chem Toxicol* 24: 329-338 (1986) (marked as **Exhibit 103**). Notably, Wehner et. al. (1986) was a study funded by Defendant PCPC (formerly known as the Cosmetic, Toiletry and Fragrance Association (CTFA), of which J&J is a member. *See* Wehner et al. (1986) at p. 329. J&J also funded other studies conducted by Wehner.

[120] Plunkett Rep. at 33-34; Singh Rep. at 57; Zelikoff Rep. at 13.

[121] Wehner et al. (1986) at p. 331.

which found that cornstarch (which is similar to talc) migrates in humans from the vagina to the ovaries and fallopian tubes.[122] Additionally, Wehner assumed that the behavior of particles would be governed by the "laws of physics" that would not permit particles to migrate "upstream." This statement was pure speculation at the time of his study and has since been disproven by the discovery of the uterine "peristaltic pump."

Rather than rely on a single animal study as J&J does, the PSC's experts rely on numerous of human migration studies discussed above, conclusions by IARC, Health Canada, and the FDA, and medical textbooks.[123] J&J's criticism that the PSC's experts failed to consider one study (even though they did consider it) is not a basis for exclusion of their opinions. The PSC's experts' migration opinions are well-supported by reliable evidence and are admissible.

3. The Scientific and Medical Literature Supports Inhalation as a Secondary Mechanism

J&J suggests that the PSC has "abandoned" inhalation as a secondary mechanism.[124] It has not.[125] J&J's other critiques of inhalation as a possible

[122] Sjosten et al. (2004) at p. 992-93, 995.

[123] *See supra* §III.A.

[124] Def. Mot. at 41.

[125] *See* Wolf Rep. at 11 ("In addition to perineal application resulting in migration and transport of particles through the genital tract, inhalation of these articles is another recognized route of exposure."); Smith Rep. at 19 ("Although migration/transport through the genital tract is the primary source of exposure with

mechanism are again over the weight of the evidence, not about admissibility. J&J does not argue that a single study relied on by the PSC's experts to support inhalation as a plausible mechanism is unreliable.

J&J's primary critique against inhalation as a secondary mechanism is that "talc" as a single entity does not cause ovarian cancer when inhaled.[126] But talcum powder products contain more than just talc. They contain asbestos and fibrous talc, which have been shown to migrate when inhaled.[127] IARC concluded that all forms of asbestos and fibrous talc (which are present in talcum powder) are Group 1 carcinogens and cause ovarian cancer through inhalation.[128] Additionally, IARC acknowledges that inhaled fibers (asbestos and others) travel to other parts of the

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genital talcum powder use, inhalation represents a secondary exposure route."); Clarke-Pearson Dep. at 217:6-11; Plunkett Rep. at 27 ("There also is evidence that application of talcum powder products results in inhalation exposure of talc dusts"); Zelikoff Rep. 13 ("Based on its physical properties talc, in a powder form, can be inhaled while being applied (EPA, 1992; IARC, 2010). Additional evidence that application of talc body powder products results in inhalation exposure of talcum powder is provided…."); Siemiatycki Rep. at 65 (recognizing migration up the genital tract and inhalation as the two possible routes of exposure).

[126] Def. Mot. at 41-45.

[127] Health Canada Draft Assessment at p. 22 ("There is a potential for inhalation exposure to talc powder during the use of certain self-care products (e.g., cosmetics, natural health products, non-prescription drugs formulated as loose powders)."); Cramer et al. (2007) (finding talc in lymph nodes suggests migration through inhalation); IARC 2012 at p. 280; Kane et al. (1996) at p. 12, 25; Wolf Rep at 11 (citing Longo et al. 2017, Steiling et al. 2018, Cramer et al. 2007, and IARC 2012).

[128] IARC 2012 at pp. 219, 232, 256, 280.

body including the lymphatic system.[129] Accordingly, the evidence on asbestos and fibrous talc is relevant.

J&J next criticizes Dr. Zelikoff for relying on animal studies that were not intended to study inhalation.[130] But that is not why Dr. Zelikoff looked at these studies. As she explained in her report, "[t]hese studies will be discussed to provide a scientific premise for the movement of particles of a certain size throughout the body."[131] J&J also misleadingly criticizes Dr. McTiernan for relying on Heller (1996–talc) as support for inhalation as a mechanism.[132] But Dr. McTiernan does not solely rely on Heller. Rather, as is clear from her report, Dr. McTiernan discuses Heller (1996–talc), along with the rest of the tissue data, including Cramer (2007),

[129] IARC 2012 at p. 280 ("The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals."); *see also* Cramer et al. 2007 (talc found in lymph nodes).

[130] Def. Mot. at 42.

[131] Zelikoff Rep. at 14-15; *see also* Steiling et al. (2018) at p. 12 (recognizing that loose powders, which include talcum powder products, "could generate such a dust cloud or atmosphere during product handling or application, and therefore there is the potential for inhalation exposure"); Health Canada Draft Assessment at p. 23 (talcum powder products particles are in the range to be inhaled and respirated).

[132] Mot. at 42-43 (citing McTiernan Rep. at 58).

which found talc particles in lymph nodes.[133] Her conclusion that these studies support inhalation as a mechanism is supported by the science.[134]

J&J's final critique of inhalation as a secondary mechanism is that other cancers also should be associated with talcum powder use.[135] However, different tissues react differently to carcinogens.[136] As Dr. Clarke-Pearson explained, "some tissues are more susceptible to a carcinogen than others."[137] Additionally, it is entirely possible that talcum powder products causes an increased risk of other cancers, but the PSC's experts were not tasked with making that determination. Nor is that required for purposes of biologically plausibility in this case.

The PSC's experts' opinions on inhalation as a secondary mechanism are reliable and admissible.

C. THE SCIENTIFIC LITERATURE SUPPORTS CHRONIC INFLAMMATION FROM TALCUM POWDER PRODUCTS AS A CAUSE OF OVARIAN CANCER

[133] McTiernan Rep. at 58-59.

[134] *See* IARC 2012 at 280 ("The route of translocation of asbestos fibres from the lungs to distant sites is unknown, although lymphatic translocation of amosite fibres deposited in the lungs has been shown in experimental animals.").

[135] Def. Mot. at 45.

[136] *See* Clarke-Pearson Dep. at 210:24-212:10.

[137] Clarke-Pearson Dep. at 212:9-10; Carson Rep. at 8 ("Because the ovaries have no intrinsic elimination system, the transport of talc particles and their constituents reaches the ovaries where it stalls and sequesters. For these reasons, ovarian tissue is most at risk for the carcinogenic effect of these substances.").

Just as it did with migration, J&J ignores the totality of the evidence and the standards of biological plausibility, and instead, argues that a handful of individual studies support its position that talc does not cause chronic inflammation. This is not a basis for exclusion under *Daubert*. The PSC's experts' opinions on chronic inflammation from talcum powder as contributing to the pathogenesis of ovarian cancer are reliable and overwhelmingly well supported by the literature. To the extent J&J disagrees with the weight of a particular study or believes it has evidence to support its position, those are matters for cross-examination and jury, not exclusion under *Daubert*.[138]

1. The Scientific Evidence Supports Talcum Powder Causes Chronic Inflammation

J&J again ignores the weight of the evidence showing that talcum powder causes inflammation and instead, selectively chooses a handful of studies on talc that J&J says do not show inflammation. The scientific evidence demonstrates that talcum powder (including all of its constituents) readily supports the conclusion that talcum powder is capable of causing chronic inflammation.[139]

Pointing to Heller et al (1996–talc), Henderson et al. (1971), and its own expert's testimony, J&J argues that inflammation is not caused by talc because it has

[138] *Daubert*, 509 U.S. at 596; *In re TMI Litigation*, 193 F.3d at 664, 665.

[139] *See supra* §III.B.

never been visually observed in pathology.[140] This has nothing to do with *Daubert*. Whether Plaintiffs are correct or J&J is correct is a matter for the jury, not an issue to be decided on *Daubert*.[141]

Nonetheless, it is well accepted that inflammation is not necessarily seen by histology in the biologic cascade resulting in carcinogenesis.[142] Oxidative stress and genetic mutations are not usually associated with histologic findings. Additionally, by the time tissue is observed, any inflammation that may have been visual would likely have been consumed by the cancer over time.[143] Still, inflammatory biomarkers like CA-125 may be observed and ovarian cancer is almost always associated with ascites which is an inflammatory consequence of ovarian cancer.[144]

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[140] Def. Mot. at 50

[141] *Milward*, 639 F.3d at 15; *Daubert v. Merrell Dow Pharm., Inc.*, 43 F.3d 1311, 1318 (9th Cir. 1995) (*Daubert* II) ("[T]he *Daubert* test "is not the correctness of the expert's conclusion but the soundness of his methodology.").

[142] Hallmarks of Cancer, Hanahan (2011) at p. 664 (authors note that inflammation is not necessarily seen by histology. Oxidative stress is not seen); Clarke-Pearson Dep. at 228:8-17 (explaining that inflammatory cascade is not necessarily visual in histology); Levy Dep. at 258:2-259:14 (explaining that whether you visually see the inflammatory response will vary from person to person and depends on timing, magnitude of inflammatory response, and methodology for detection, including a ROS assay).

[143] Kane Rep. at 12 ("Remote exposure will not necessarily mean there will be evidence of current inflammation or foreign body reaction when tissues are examined.").

[144] Clarke-Pearson Dep. at 226:18-227:5.

J&J also critiques a handful of animal studies relied on by the PSC's experts as only showing acute inflammation, not chronic inflammation. To be clear, the PSC's experts do not simply rely on animal studies.[145] Additionally, Keskin (2009) involved rats and application of talc (asbestos-free) only for only three months.[146] Given the study limits in Keskin (2009), it is not surprising that only infection and acute granulomas were shown.[147] The PSC's experts' opinions have to do with human females with long-term use of talcum powder (which also contains platy talc, asbestos, fibrous talc, heavy metals, and other chemicals. Despite the limited timeframe in Keskin, the study authors still noted "foreign body reaction" and "increase in inflammatory cells" in all of the exposed rats.[148] While chronic

[145] *See supra* §III.B. (discussing in vitro and in vivo studies); Clarke-Pearson Rep. at 4; Smith Rep. at 17; Wolf Rep. at 12; Carson Rep. at 6; Singh Rep. at 58; Zelikoff Rep. at 25; McTiernan Rep. at 60-61; Plunkett Rep. at 42; Moorman Rep. at 33-34.

[146] Keskin et al. (2009) at p. 925; *see* Health Canada Draft Assessment, p. 16 ("while no cancer or pre-cancer effects were observed, Keskin and colleagues (2009) noted that the study duration may have been too short to note these types of effects.").

[147] Health Canada Draft Assessment, p. 15 ("Ovarian epithelial tumours are also rare in these animals (Taher et al. 2018). Ovarian tumours do occur in some strains of mice and rats; however, the low incidence and/or the length of time required for the appearance of tumours renders them poorly feasible for experimental studies of ovarian carcinogenesis Vanderhyden et al. "Animal models of ovarian cancer", *Reproductive Biology and Endocrinology* 2003, I:67. (attached as **Exhibit 104**). On account of the limitations detailed above, in addition to the challenges posed by exposing animals via the perineal route, animal data are very limited.").

[148] *Id.*

inflammation was not seen in the limited study time, the study results are consistent with the conclusion that talcum powder can cause chronic inflammation.

Finally, J&J's attack on Dr. Saed for citing Langseth (2004) is unavailing.[149] Dr. Saed mistakenly cited Langseth (2004) instead of Langseth (2008), which is an animal study. Even so, Dr. Saed's citation to Langseth is for the general proposition that "[s]tudies that exposed lab animals (rats, mice, and hamsters) to asbestos-free powder in various ways have mixed results, with some showing tumor formation and others finding only inflammation."[150] This general premise is not disputed and Dr. Saed also cites Graham, J. & Graham, R. Ovarian cancer and asbestos. Environ Res 1, 115-128 (1967), which does involve hamsters and mice and demonstrates inflammatory processes.

Finally, J&J footnotes the argument that inflammation does not occur because if it did inflammation would also occur in other parts of the genital tract such as the vagina, cervix, and endometrium. Mot. at 54 n.122. As the PSC's experts explained, these different areas (e.g., vagina) have different tissues and different tissues react differently to carcinogens.[151] Additionally, there is the issue of time. Unlike with the

[149] Def. Mot. at 53.

[150] Expert Report of Ghassan Saed, Ph.D. (November 16, 2018) at 10-11. (attached as **Exhibit 105**).

[151] Clarke-Pearson Dep. at 212:21-23; Carson Rep. at 8 ("Because the ovaries have no intrinsic elimination system, the transport of talc particles and their constituents reaches the ovaries where it stalls and sequesters."); Wehner et al. (1994) at p. 1176

ovary, there is no evidence that the talcum powder particles lodge in cervical or endometrial tissue on the way to the fallopian tubes and ovaries, which would result in chronic inflammation.[152]

The totality of the scientific evidence reliably supports the PSC's experts' opinions that talcum powder can cause chronic inflammation that leads to an increased risk of ovarian cancer.

2. The Scientific Evidence Supports the Opinion that Chronic Inflammation Increases the Risk of Ovarian Cancer

J&J again ignores the evidence and argues that the PSC's experts' opinion that inflammation leads to ovarian cancer is "nothing other than unsubstantiated hypotheses and vague generalities."[153] J&J claims that the "theory" that inflammation can cause ovarian cancer first appeared in a review article in 1999 and has yet to be proven.[154] Not so.

Ness and Cottreau (1999) did not pull the idea that inflammation plays an important role in the pathogenesis of ovarian cancer out of thin air. Inflammation as

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("[T]he ovarian surface epithelium is a dynamic tissue with distinct morphological differentiations: it may proliferate inwards and form crypts and inclusion cysts or it may develop superficial papillary excrescences.").

[152] Carson Dep. at 198:19-199:7, 209:15-210:1.

[153] Def. Mot. at 54.

[154] Def. Mot. at 55

a mechanism of cancer has been well known for decades.[155] Ness and Cottreau did a thorough analysis of the available data on inflammation and cancer and the mechanisms known to relate to ovarian cancer, and concluded in 1999 that various inflammatory factors, including exposure to asbestos and talcum powder, are epithelial inflammation initiators that play a role in ovarian carcinogenesis.[156]

Subsequent scientists have done additional research and concluded that inflammation plays a critical role in the pathogenesis of epithelial ovarian cancer. For example, in 2009 Shan and Liu found that "[t]he tumor milieu in which EOC develops has been described as one enriched with a broad spectrum of pro-inflammatory cytokines and chemokines…Increasing evidence suggests that inflammation contributes significantly to the etiology of EOC;" in 2014 Trabert et al. found "evidence that inflammation plays an important role in ovarian carcinogenesis;" and in 2018, Health Canada found that [t]here is support for an association of inflammation and increased risk of ovarian cancer" and Savant et al.

[155] *See* Balkwill and Mantovani (2001) at p. 539 (recognizing that as far back as 1863, inflammatory cells (leukocytes) were identified in tumor tissue).

[156] Ness and Cottreau (1999) at p. 1464 (discussing review of the data on inflammation).

(2018) "presented published evidence suggesting that inflammation and inflammatory mediators promote ovarian tumorigenesis."[157]

J&J ignores the vast majority of relevant and reliable evidence supporting inflammation as a mechanism of ovarian cancer. Instead, discussing only two studies (Trabert and Buz'Zard), J&J takes issue with them as being "inconclusive" and having methodological flaws, respectively.[158] *First*, even though the results of Trabert's study were inconclusive the authors recognized that "[m]ultiple lines of evidence suggest that ovarian cancer may be related to chronic inflammation…[I]nflammation-related exposures such as endometriosis and exposure to talc or genital powder and asbestos have been associated with increased ovarian risk."[159]

Second, J&J's critiques of Buz'Zard for using granulosa cell lines, immortalized lines, and not showing dose response are without merit. Buz'Zard used both granulosa *and* epithelial cells and found that "ROS generation increased with

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[157] *See* Shan and Liu (2009) at p. 3130; Trabert et al. (2014-inflammation markers) at pp. 309; Health Canada Draft Screening Assessment at p. 18; Savant et al. (2018) at p. 18; *see also* Freedman et al. (2004) at p. 4; Saed et al. (2017) at pp. 596-97.

[158] Def. Mot. at 57-60.

[159] Trabert et al., "Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory Drug, and Acetaminophen Use and Risk of Invasive Epithelial Ovarian Cancer: A Pooled Analysis in the Ovarian Cancer Association Consortium," *JNCI J Natl Cancer lnst.* 106(2): 1-11, at p. 1 (2014) (attached as **Exhibit 106**).

time in the talc treated [normal] cells."[160] J&J provides no explanation for why the use of immortalized cells eliminates these results. Based on this data, the authors concluded that "[t]he data show that talc is capable of increasing cell proliferation, inducing neoplastic transformation of both the normal stromal and epithelial ovarian cells *in vitro*; and increasing ROS generation in these cells as well as the PMN cells."[161] Additionally, as to cellular transformation, the authors explained: "Our data show talc not only increased cell viability (Fig. 1A), but also caused an increased in transformed cells in both the stromal *and* epithelial ovarian cells by their ability to grow, divide and form colonies while being suspended in soft agar."[162] These results are relevant.

J&J also criticizes some experts for citing studies regarding the role anti-inflammatories ("NSAIDs") play in decreasing cancer risk.[163] J&J argues that because the results of the NSAID studies are mixed, the PSC's experts cannot rely on them. The PSC's experts do not rely on NSAID data for their opinions on inflammation – they rely on the overwhelming body of evidence that demonstrates inflammation plays an important role in the pathogenesis of ovarian cancer. The

[160] Buz'Zard and Lau (2007) at p. 582.

[161] *Id.* at p. 585.

[162] *Id.* at p. 584.

[163] Def. Mot. at 64.

PSC's experts that cite to the NSAID data acknowledge its mixed results and only cite it as additional evidence of the role of inflammation in cancer pathogenesis generally.[164] The evidence supports this opinion.

J&J selected a single article (Trabert (2014-NSAIDs) on the relationship between anti-inflammatory medications and labeled it "flawed" and "inconclusive." This study was conducted by the Ovarian Cancer Cohort Consortium, a prestigious group of researchers (acknowledged by Dr. Birrer who is a member) and including close to 40 authors.[165] J&J rejects the conclusions of these respected scientists and ignores the remainder of the literature on this topic. Trabert's NSAID study observed a 20% risk reduction for daily users of aspirin and 34% risk reduction for regular users of low-doses of aspirin.[166] The study did not find any substantial differences

[164] *See* Wolf Rep. at 12 ("Although the literature is still somewhat contradictory, aspirin and other non-steroidal anti-inflammatory drugs have been shown to prevent and treat certain types of cancer, particularly colorectal."); Smith Rep. at 18 ("Although somewhat inconsistent, data regarding NSAID and aspirin suggest a protective effect…No study found an effect on ovarian cancer…."); Levy Rep. at 12-13 ("The earlier studies with a focus on NSAIDs were preliminary and results were somewhat inconsistent."); McTiernen Rep. at 60 (citing NSAID data for "f[]urther evidence of the inflammation mechanism"); Kane Rep. at 12 ("There also are some studies showing a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect.").

[165] Trabert et al. (2014) (NSAIDs).

[166] *Id.* at p. 5.

between histologic subtypes of ovarian cancer.[167] The authors identified inflammation reduction as a plausible mechanism.[168]

In the same year (2014), Trabert et al. also performed a case-control study measuring 46 inflammation-related biomarkers in ovarian cancer cases and matched controls.[169] In this study, the researchers identified several circulating inflammation markers that were associated with risk of developing cancer between 2 and 14 years later.[170] The authors again identify inflammation as plausible mechanism.[171]

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[167] *Id.* at p. 6.

[168] *Id.* ("Several established risk factors for ovarian cancer are related to inflammatory processes. During ovulation, follicles rupture and inflammatory mediators are released locally that may initiate cell transformation or that may promote growth of transformed cells. Proinflammatory agents are also released in inflammatory processes related to endometriosis. Aspirin and nonaspirin NSAIDs may reduce exposure to these inflammatory processes; thus, the reduced risk of ovarian cancer with frequent aspirin use and nonsapirin NSAID use is consistent with the hypothesized inflammatory etiology of ovarian cancer.") (citations omitted).

[169] Trabert et al. (2014-inflammation markers).

[170] *Id.* at p. 6.

[171] *Id.* at p. 2 ("Epidemiologic evidence implicates chronic inflammation as a central mechanism in the pathogenesis of ovarian cancer, the most lethal gynecologic cancer among women in the United States. Chronic inflammation can induce rapid cell division, increasing the possibility for replication error, ineffective DNA repair and subsequent mutation. Ovarian cancer has been linked to several events and conditions which are related to inflammation and repair, including incessant ovulation, endometriosis, exposure to talc and asbestos, and in some studies pelvic inflammatory disease. In addition, reduced risks found for aspirin use could be related to direct anti-inflammatory actions, while reduced risks related to tubal ligation and hysterectomy could reflect limited exposure to environmental causes of inflammation.") (citations omitted).

Trabert and the Ovarian Cancer Cohort published a pooled analysis of 12 case-control studies in 2019, confirming the slightly lower but statistically significant, risk decrease in ovarian cancer risk with regular aspirin use – similar to the risk reduction observed in case-control analyses.[172] The authors again identify inflammation as plausible mechanism.[173]

Additionally, a study of analgesic medication use and the risk of epithelial ovarian cancer in African American women, published in 2016, recognized the inconsistency in the literature, "with the majority of studies showing an inverse association."[174] In this study, aspirin use, overall, was associated with a 44% lower EOC risk.[175] The authors concluded that this study "supports previous evidence that any NSAID use, but not acetaminophen [not an anti-inflammatory agent] is inversely associated with EOC risk.[176] These authors also identified inflammation as a

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[172] Trabert et al., "Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium," *J Nat Cancer Inst.* 111(2): 1-9, at p. 8 (2019) (attached as **Exhibit 107**).

[173] *Id.* at p. 2. "Chronic inflammation likely plays a key role in ovarian carcinogenesis. Factors associated with epithelial disruption through ovulation, inflammation-related exposures such as endometriosis and pelvic inflammatory disease, and circulating biomarkers of inflammation have been associated with ovarian cancer risk.")

[174] Peres et al., "Analgesic medication use and risk of epithelial ovarian cancer in African American women," *British J. of Cancer* 114: 819-825 (2016) (attached as **Exhibit 108**).

[175] *Id.* at p. 819.

[176] *Id.* at p. 824.

plausible mechanism. These authors also identify inflammation as the plausible mechanism.[177] Although research is ongoing regarding the role of anti-inflammatory agents in reduction of ovarian cancer risk, these studies support the importance of inflammation in the etiology of epithelial ovarian cancer.

Finally, J&J's critiques of the evidence on pelvic inflammatory disease ("PID") have no merit. PID is frequently recognized as a risk factor for epithelial ovarian cancer, although the data indicates that the association may be specific to histologic subtype. A systematic review and pooled analysis published in 2016 found that PID was associated with an increased risk of serous and mucinous borderline ovarian tumors.[178] The authors concluded that "[a]n association between PID and the risk of ovarian tumors is biologically plausible and could be explained by the inflammation hypothesis. Inflammation is characterized by the production of free radicals, cytokines, prostaglandins, and growth factors with the potential for genetic

[177] *Id.* at 820 "Inflammation may play a role in ovarian cancer carcinogenesis through the production of toxic oxidants and bioactive substances, increasing the chances of DNA damage and mutagenesis. Analgesic drugs, such as aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs), have anti-inflammatory properties and have been associated with reduced risks of several malignancies.) (citations omitted).

[178] Rasmussen et al., "Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies," *Am J Epidemiol.* 185(1): 8–20 (2017) (attached as **Exhibit 109**).

and epigenetic changes to the DNA, resulting in an increased risk of malignant transformation.[179]

Similarly, a large population-based cohort study published in 2018 found a statistically significant increased risk of high grade serous carcinoma.[180] The authors concluded that their "finding that PID was associated with an increased risk of HGSC lends support to the hypothesis that inflammatory processes play a role in the development of HGSC." That PID is associated with ovarian cancer is consistent with inflammation from talcum powder also increasing the risk of ovarian.

D. THE SCIENTIFIC EVIDENCE SUPPORTS THE OPINION THAT TALCUM POWDER CAUSES OVARIAN CANCER BY LOWERING MUCI ANTIBODIES

[179] *Id.* at 14

[180] Stewart et al., "Risk of high-grade serous ovarian cancer associated with pelvic inflammatory disease, parity and breast cancer," *Cancer Epidemiology* 55: 110-116 (2018) (attached as **Exhibit 110**).

Citing their own experts' opinions but **no** scientific evidence,[181] J&J argues that the MUC1 "theory" is unsupported.[182] J&J ignores the peer-reviewed literature that describes the role of MUC1 as a plausible inflammatory mechanism by which talcum powder exposure can contribute to ovarian cancer.

"Mucins are proteins involved in the formation of mucous barriers on epithelial surfaces."[183] MUC1 – the surface glycoprotein human mucin 1 – is

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[181] J&J's repeatedly attempts to persuade the Court by citing the opinions of its own experts is improper. All J&J has accomplished in doing so is to illustrate that its *Daubert* challenge is not about methodology but more about winning a proverbial "battle of the experts" before it has to present its case to a jury. Of course, such battles are for the jury to decide, not the Court. *See S.E.C. v. Lucent Techs., Inc.*, 610 F. Supp. 2d 342, 351 (D.N.J. 2009) (quoting *Oddi v. Ford Motor Co.*, 234 F.3d 136, 146 (3d Cir. 2000)); *Dzielak v. Whirlpool Corp.*, No. CV2120089KMJBC, 2017 WL 1034197, at *26 (D.N.J. Mar. 17, 2017). *Lansford-Coaldale Joint Water Auth. v. Tonolli Corp.*, 4 F.3d 1209, 1216 (3d Cir. 1993) ("'[I]n a battle of the experts, the factfinder 'decide[s] the victor.'") (alteration in original) (quoting *Mendes-Silva v. United States*, 980 F.2d 1482, 1487 (D.C. Cir. 1993))); *Dzielak*, 2017 WL 1034197, at *26; *In re Biogen '755 Patent Litig.*, No. CV102734CCCJBC, 2018 WL 3586271, at *11 (D.N.J. July 26, 2018); *Lanzilotti by Lanzilotti v. Merrell Dow Pharm. Inc.*, No. CIV.A. 82-0183, 1986 WL 7832, at *3 (E.D. Pa. July 10, 1986) (the experts for both sides differed as to what interpretations should be given to various data. 'The case was thus a classic battle of the experts, a battle in which the jury must decide the victor.'); *Tyco Healthcare Grp. LP v. Mut. Pharm. Co., Inc.*, No. 07CV1299SRCCLW, 2016 WL 3965201, at *4 (D.N.J. July 22, 2016); *In re Gabapentin Patent Litig.*, No. CIV.A. 00-2931, 2011 WL 12516763, at *10 (D.N.J. Apr. 8, 2011) (concluding that defendants' critiques of plaintiffs' experts' methodology and inconsistent conclusions presented "a battle of the experts, and both sides will be permitted to present expert testimony on these issues and to cross-examine the other side's expert witnesses."); *Dzielak*, 2017 WL 1034197, at *26.

[182] Def. Mot. at 66-67.

[183] Health Canada Draft Assessment, at p. 19.

expressed in high levels by ovarian cancer.[184] "It is known that women with ovarian cancer who have anti-MUC1 antibodies survive longer."[185] Accordingly, anti-MUC1 antibodies appear to have a protective effect against ovarian cancer.[186]

The Cramer et al. 2005 study looked at whether anti-MUC1 antibodies reduce the risk of ovarian cancer.[187] The study authors found that the use of talcum powder in the perineal area was associated with significantly decreased levels of antibodies to MUC1.[188] Cramer later opined that "many risk factors for ovarian cancer may be explained by their ability to raise or lower MUC1 immunity."[189] Because talcum powder use was "a factor that lowered anti-MUC1 antibodies," Cramer concluded that "rather than a direct carcinogenic effect on ovarian epithelium, immune dysregulation involving MUC1 may be induced by chronic talc use that may lower protective immunity."[190]

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[184] *Id.*; Cramer et al. (2007), at p. 500.

[185] Cramer et al. (2007), at p. 500.

[186] Health Canada Draft Assessment, at p. 19.

[187] Cramer et al., "Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer," *Cancer Epidemiol Biomarkers Prev* 14(5): 1125-1131, at p. 1125 (2005) (attached as **Exhibit 111**).

[188] *Id.* at 1128.

[189] Cramer et al. (2007), at 501.

[190] *Id.*

J&J ignores this evidence and instead criticizes Dr. Zelikoff's reliance on Karageorgi et al. (2010).[191] J&J claims that Karageorgi (2010) is inapplicable because that study was about endometrial cancer. But the results of Karageorgi (2010) related to MUC1 were not unique to endometrial cancer – they were applicable to MUC1 generally. The study authors concluded that "[u]sers of talcum powder have lower plasma levels of anti-MUC1 antibodies than non-users."[192] Karageorgi also found a statistically significant increase risk of endometrial cancer associated with perineal talcum powder used and proposed an inflammatory mechanism.[193] This conclusion is consistent with Cramer et al. 2005, Cramer et al. 2007, and Health Canada, which Dr. Zelikoff considered.[194]

Accordingly, the PSC's experts' opinions regarding MUC1 are reliable and supported by the evidence.

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[191] Def. Mot. at 67.

[192] Karageorgi et al., "Perineal use of talcum powder and endometrial cancer risk," *Cancer Epidemiol Biomarkers Prev.* 19(5): 1269-1275, at p. 1273 (2010) (attached as **Exhibit 112**).

[193] "Other mechanistic factors that may come into play include chronicity of inflammation (34) and timing of exposure with regard to the phases of the uterine cycle. Any inflammation initiated by genital application of talc is likely to be sustained, since studies indicate that women start using talcum powder at an early age (35) and continue using it for decades (14). The endometrial tissue is highly proliferative and regenerates with every menstrual cycle. Chronic inflammation following long duration of use of talcum powder may be sufficient to cause carcinogenesis despite the monthly shedding of the endometrial lining." *Id.*

[194] Zelikoff Rep. at reliance list; Cramer et al. 2005 is also cited by Karageorgi et al.

V. DR. ZELIKOFF'S OPINIONS ARE RELIABLE

Finally, J&J seeks to exclude Dr. Zelikoff's entire opinion as unreliable due to what J&J characterizes as "rampant plagiarism."[195] Dr. Zelikoff is a well-qualified toxicologist[196] and, as explained above, her opinions on biological plausibility are reliable. Her admitted oversight in fully quoting from sources identified in her expert report does not negate the reliability of her opinions.

An accusation of plagiarism goes to an expert's credibility, not admissibility, and is "better left to the trier of fact."[197] Absent proof that the alleged plagiarism has affected the reliability of the expert's opinion, the opinion should be admitted.[198]

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[195] Def. Mot. at 69.

[196] *See The Plaintiffs' Steering Committee's Memorandum In Response And Opposition To Johnson & Johnson And Johnson & Johnson Consumer Inc.'s Motion To Exclude Plaintiffs' Experts' Opinions Regarding Alleged Heavy Metals And Fragrances In Johnson's Baby Powder And Shower-To-Shower.*

[197] *Legier & Materne v. Great Plains Software, Inc.*, No. 03-0278, 2005 U.S. Dist. LEXIS 17686, *10-12 (E.D. La. Aug. 3, 2005); *see also Ji v. Bose Corp.*, 538 F. Supp. 2d 354, 359 (D. Mass. 2008) (citing *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993) ("personal reliability questions …go to…credibility and are for the jury to decide.").

[198] *See In re Processed Egg Products Antitrust Litigation* No. 08-MD-2002, 2016 WL 4547207, at *5 (E.D. Pa. Aug. 31, 2016) ("some quotations alone are not enough to call into question the reliable of [the expert]'s entire report"); *GWTP Investments, L.P. v. SES Americom, Inc.*, No. 3:04-CV-1383-L, 2007 WL 7630459, at *5 (N.D. Tex. Aug. 3, 2007) (refusing to exclude expert opinion based on plagiarism where defendant "has not shown that it impacts the reliability" of the opinion).

Here, the portions of Dr. Zelikoff's alleged to be plagiarized are background information and points of common knowledge pulled from various sources.[199] J&J fails to show how this makes her opinions as a whole unreliable. Dr. Zelikoff's analysis of the facts related to this case and her opinions are all her own.[200] Dr. Zelikoff's credibility should be left to the jury.

Moore v. BASF Corp., No. 11-1001, 2012 WL 6002831, at *7 (E.D. La. Nov. 30, 2012), relief on by J&J, is distinguishable because in *Moore*, the expert's "conclusions as to the [required] warnings …were copied verbatim from the report of another expert." *Id.* at *20. Dr. Zelikoff's analysis and conclusions as written in her report are all her own. The expert in *Moore* also offered dishonest testimony that the report was his own writing and that he had not consulted with other experts. *Id.* To the contrary, Dr. Zelikoff testified that her analysis and conclusions were her own and admitted and explained her citation errors.

VI. CONCLUSION

For the foregoing reasons, J&J's motion to exclude the PSC's experts' opinions related to biological plausibility should be denied in its entirety.

[199] *See* Zelikoff Dep. at 75:22-76:7, 109:24-111:22, 119:22-121:13.

[200] *Id.* at 95:7-95:14.

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